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Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977.* Edinburgh, London: Churchill Livingstone, 1978: 16–26.

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Presentation Slow-Trasicor tablets each contain 160mg oxprenolol hydrochloride BP in a special sustained-release formulation available in simple daily reminder packs of 28 tablets. **Dosage in hypertension** Initially one or two tablets in the morning. **Dosage in angina** Initially one or two tablets in the morning. An evening dose may be beneficial in nocturnal angina. As with other beta-blocking drugs, sudden withdrawal of treatment may induce severe and continuous angina. Patients should, therefore, be advised to avoid interruption of established therapy and if withdrawal becomes necessary it should be done gradually. **Side effects** Dizziness, drowsiness, headache, insomnia, excitement and gastro-intestinal disturbance may occur and, rarely, isolated cases of excessive bradycardia. Beta-blockers are occasionally associated with skin rashes and/or dry eyes. If any such reaction is suspected, treatment should be withdrawn gradually. **Precautions** If there is evidence of cardiac failure this must be controlled by digitalis and/or diuretics before and during Slow-Trasicor therapy. Should the pulse rate fall below 50 per minute, then treatment should be restarted at a lower dose. Caution should be observed when treating asthmatics, chronic bronchitics or other individuals where bronchospasm may be provoked. Slow-Trasicor should be given cautiously to patients with alcoholism, metabolic acidosis, during pregnancy or anaesthesia with ether or chloroform. Beta-blockers can mask symptoms of hypoglycaemia and also affect carbohydrate metabolism. It may therefore be necessary to readjust the insulin requirements in diabetic patients. Occasionally hypotension may occur with higher dose levels. **Contra-indications** Patients with atrio-ventricular block, marked bradycardia and cardiogenic shock. **Packs** Cartons of 28 Slow-Trasicor tablets consisting of two reminder calendar foils of 14. Basic NHS price £6.66 PL0008/0130 PA 28/7/1 Full prescribing information is available on request from CIBA Laboratories, Horsham, West Sussex.
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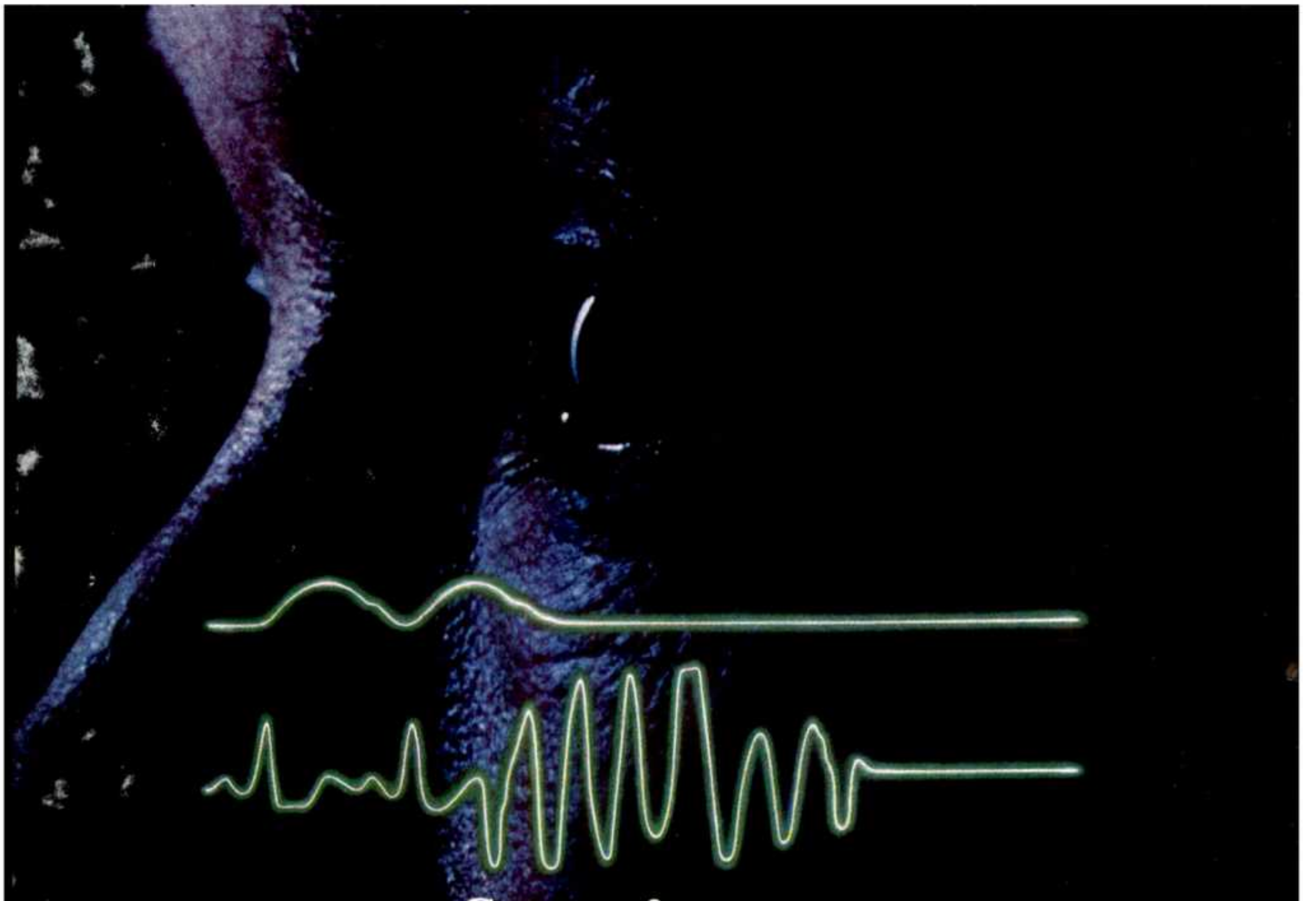

Sometimes, hypertension resolves of its own accord

The risk of sudden death is a constant companion for hypertensive patients who also have ischaemic heart disease.

Indeed, sudden death is the first symptom of unsuspected coronary artery disease in as many as 20% of cases.[1]

Sotazide is a new antihypertensive treatment whose qualities make it particularly suitable for long-term antihypertensive therapy.

The beta-blocker component, sotalol, has an inherent long action which gives it round-the-clock antihypertensive and anti-arrhythmic activity on once daily dosage. In addition to reducing sympathetic drive, sotalol is unique in possessing class III anti-arrhythmic activity which is particularly relevant in diminishing the risk of ventricular fibrillation.

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New once-daily

Sotazide*

Sotalol hydrochloride and hydrochlorothiazide

Precise and predictable control of hypertension

cribing Information

SENTATION Tablets containing 160mg sotalol hydrochloride and 25mg hydrochlorothiazide. **USES** The management of mild or lerate hypertension. **DOSAGE AND ADMINISTRATION Initial Dose**: one Sotazide tablet per day. **Range**: 1-4 tablets per day. **NTRAINDICATIONS, WARNINGS, ETC.** SOTAZIDE should not be used where there is evidence of heart block, history of bronchospasm, etic keto-acidosis, impending or uncontrolled cardiac failure, anaesthesia that produces myocardial depression; hypersensitivity to lol, hydrochlorothiazide or sulphonamide derivatives. Use with caution in treated diabetes, hepatic/renal disease. See Data Sheet for ils, including use in anaesthesia. Safe use in pregnancy has not been established. SOTAZIDE should not be given to patients with iac decompensation unless incipient or established heart failure is controlled. At the first sign of impending cardiac failure or the ression of failure, SOTAZIDE dosage should be reduced or discontinued. The dosage of SOTAZIDE should be decreased or therapy ntinued if the pulse rate falls below 50 beats/minute. Sudden withdrawal of treatment with beta blockers in hypertensive patients angina pectoris has induced severe and continuous angina in some cases. Although this effect has not been observed with SOTAZIDE, ld such a reaction occur, SOTAZIDE treatment should be reinstituted and then withdrawn gradually by reducing the dosage over a od of weeks. All patients receiving hydrochlorothiazide (as in SOTAZIDE) therapy should be checked periodically for clinical signs of or electrolyte imbalance. Hydrochlorothiazide may reduce serum protein bound iodine without producing symptoms of thyroid rbance. **SIDE EFFECTS** Dyspnoea, tiredness, dizziness, light-headedness, headache, fever and excessive bradycardia have been rted with sotalol. Most of these side effects are transient or disappear when the dosage is reduced. There have been reports of skin rashes or dry eyes associated with the use of beta-adrenergic blocking drugs. In most cases the symptoms have cleared when the treatment was withdrawn. Gradual discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Hyperuricaemia has been observed with thiazides but clinical gout is rare. Photosensitivity, anaphylactic reactions and depression of the formed elements of the blood have been reported rarely with thiazides. **OVERDOSAGE** If excessive bradycardia (and/or hypotension) occurs, atropine 0.5 to 2.0mg should be given intravenously, immediately followed, if necessary, by a beta receptor stimulating agent such as isoprenaline intravenously, 5mcg/minute up to 25mcg initially. **LEGAL CATEGORY** POM. **PACKAGE QUANTITIES SOTAZIDE tablets**: units of 28 – blister strips of 14 tablets with 2 strips per carton. **BASIC NHS PRICE** Sotazide compliance pack of 28 tablets £6.78. **PRODUCT LICENCE NUMBER SOTAZIDE tablets**: 0125/0113.

References 1. Kannel WB, Doyle JT, McNamara PM et al. Precursors of sudden coronary death. *Circulation* 1975; 51(4): 606-613. **2.** Sundquist H, Anttila M, Simon A, Reich JW. Comparative bioavailability and pharmacokinetics of sotalol administered alone and in combination with hydrochlorothiazide. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 565-570. **3.** Jaattela A. The combination of sotalol and hydrochlorothiazide in the treatment of hypertension. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 557-564. **4.** Basson W, Myburgh DP. Synergism of a beta blocker and a diuretic in the once-a-day treatment of essential hypertension. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 571-578. **5.** Reynaert J. Once-a-day treatment with sotalol and hydrochlorothiazide in patients with essential hypertension. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 579-583. **6.** Monsalvo HJ. Sotalol/hydrochlorothiazide in geriatric hypertensive patients. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 584-590. *Trademark. Authorised User. Further information is available to the medical profession on request.

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Dosage: 100mg daily. **Contraindications:** Heart block. **Precautions:** Untreated cardiac failure, bradycardia, renal failure, anaesthesia and pregnancy. 'Tenormin' is Beta$_1$ selective and can be used with caution in obstructive airways disease. **Side Effects:** Coldness of extremities and muscular fatigue. Sleep disturbances rarely seen. Rashes and dry eyes have been reported with beta-blockers – consider discontinuance if they occur. Cessation of therapy with a beta-blocker should be gradual. **Pack size and basic NHS price:** 28's £6.46. **P.L.** 0029/0122.

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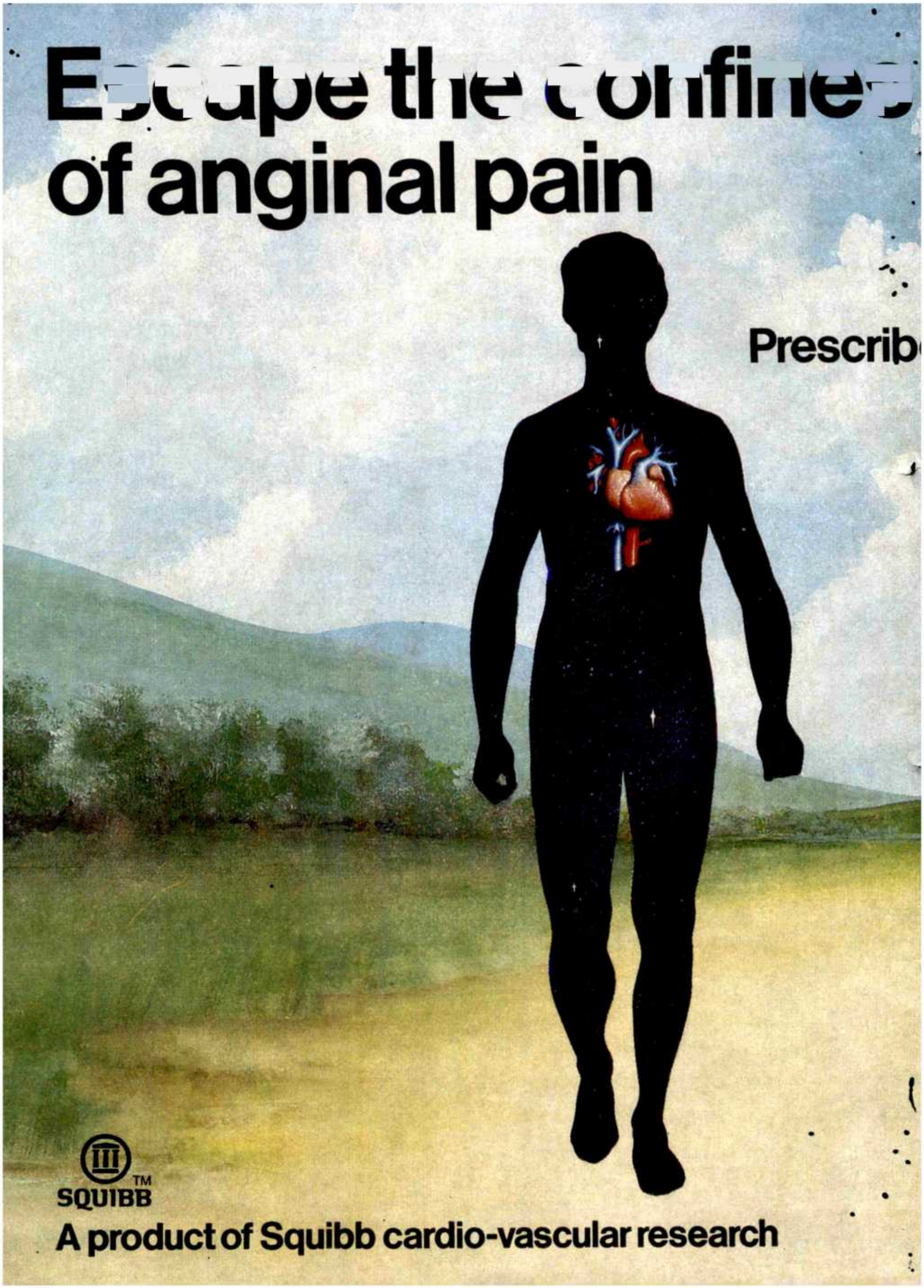

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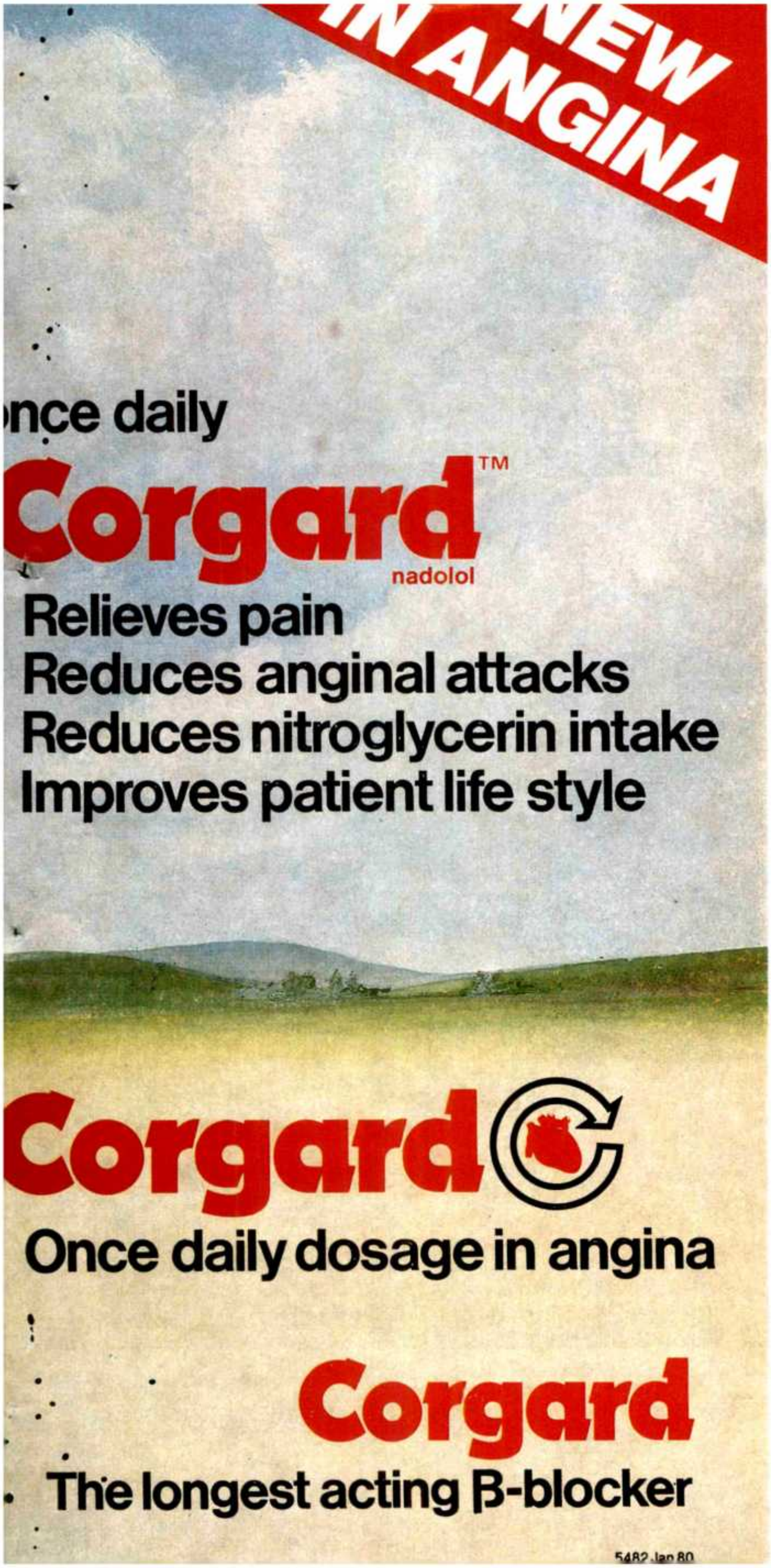
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Presentation
White round biconvex tablets. 80 mg: scored on one side and engraved "Squibb" '241' containing nadolol 80 mg. 40 mg: engraved "Squibb" '207' containing nadolol 40 mg.

Indications
Corgard is indicated in the long-term management of angina pectoris and hypertension.

Dosage and administration
Dosage should be individually titrated. In elderly patients, particularly those with angina pectoris, a low initial dose should be used so that sensitivity to side effects may be assessed.
Nadolol may be given in a once daily dosage without regard to meals.
Angina Pectoris: Initially 40 mg once daily. This may be increased at weekly intervals until an adequate response is obtained or excessive bradycardia occurs. Most patients respond to 160 mg or less daily.
The value and safety of daily doses exceeding 240 mg have not been established.
Hypertension: Initially 80 mg once daily. This may be increased by a weekly increment of 80 mg or less until an optimum response is obtained. Most patients respond to 240 mg or less, daily, but doses up to 640 mg have been required for a few patients. In some patients it is necessary to administer a diuretic, peripheral vasodilator and/or other anti-hypertensive agent in conjunction with nadolol in order to achieve satisfactory response.
Treatment of hypertension associated with phaeochromocytoma may require the addition of an alpha-blocking agent.

Contra-indications
Bronchial asthma, sinus bradycardia and 2nd and 3rd degree heart block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure.

Warnings
The normal precautions associated with the use of beta-adrenergic blockers should be followed.
Exacerbation of angina and myocardial infarction have occurred after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with angina pectoris or other evidence of coronary artery insufficiency.
When discontinuing long-term nadolol therapy the dosage should be reduced gradually over a period of at least two weeks.
There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable.
Caution is advised in the presence of impaired renal or hepatic function, obstructive airways disease and diabetes mellitus.
Care should be taken in administering nadolol during and within 2 weeks of administration of adrenergic augmenting psychotropic drugs such as monoamine oxidase inhibitors.
The safety of nadolol in pregnancy has not yet been established, and nursing mothers should only receive nadolol if deemed essential.

Side-effects
These resemble those reported with other beta-blocking drugs and rarely require withdrawal of treatment. Those reported infrequently include gastro-intestinal effects, bradycardia, fatigue, light-headedness, cold extremities, insomnia, paraesthesia and dryness of the mouth. Cardiac insufficiency, hypotension and AV block have occurred on rare occasions. Overdosage or exaggerated response should be treated supportively and symptomatically.

Legal category
Prescription only.

Product Licence Numbers
80 mg – 0034/0186
40 mg – 0034/0185

Package quantities
Bottles of 100 tablets.
Average daily cost of treatment 16p per day.

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Prescribing Information

Presentation Orange, soft gelatin capsule containing yellow viscous liquid. Each capsule contains 10mg nifedipine. **Uses** *Mode of Action* Adalat is a potent calcium antagonist. Its most important effect is to protect the heart against excessive oxygen utilisation during physical activity. There is a reduction in cardiac work and in myocardial oxygen demand. Adalat also causes peripheral vasodilatation and thus reduces peripheral resistance and heart work load. Adalat has no therapeutic anti-arrhythmic effect. Since Adalat does not cause a rise in intraocular pressure, it can be used in patients with glaucoma. *Indications* For the treatment and prophylaxis of angina pectoris. **Dosage and Administration** For oral administration, the capsules should be taken with a little fluid during or after meals. The recommended dose is one 10mg capsule three times daily. If necessary, up to two capsules three times daily may be taken. Treatment may be continued indefinitely. If an immediate effect is required, the capsule should be bitten open and the liquid contents allowed to remain in the mouth. **Contra-indications** Must not be given to women capable of child-bearing. **Warnings and Precautions** Adalat is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8-10 days. Adalat may be used in combination with beta-blocking drugs and other antihypertensive agents, but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Adalat will not prevent possible rebound effects after cessation of antihypertensive therapy. Adalat should be used with caution in patients whose cardiac reserve is poor. Ischaemic pain has been reported in some patients, commonly within 30 minutes of the introduction of Adalat therapy. Patients experiencing this effect should discontinue Adalat. The use of Adalat in diabetic patients may require adjustment of their control. There is no known drug incompatibility. **Side effects** Adalat is well tolerated. Minor side-effects, usually associated with vasodilatation are mainly headache, flushing and lethargy. These are transient and invariably disappear with continued treatment. **Overdosage** Standard measures such as atropine and noradrenaline may be used for resultant bradycardia and hypotension. Intravenous calcium gluconate may be of benefit. **Pharmaceutical Precautions** The capsules should be protected from strong light and must be stored in the manufacturer's original container. **Legal Category** POM. **Pack Quantities and Basic NHS Cost** Adalat is available in foil packs of 100 capsules. Daily treatment cost 36p (3 capsules ex 100). **Further Information** Nil. **Product Licence Number** PL0010/0021; Republic of Ireland: PA 21/3/1.

Additional prescribing information on Adalat (nifedipine) is available from:
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Br Heart J 1980; **44:** 1–4

Future of computerised electrocardiography

FRITS L MEIJLER, ETIENNE O ROBLES DE MEDINA, JAN C HELDER

From the Department of Cardiology and Central Computer Department, University Hospital, Utrecht, The Netherlands

SUMMARY The advent of computerised electrocardiography has been of prime importance for the storage and retrieval of data, but none of the available systems is of universal application for analysis of patterns. Future needs require hierarchical systems of increasing degrees of complexity, depending on the source of requests, and there should be appropriate provision for review by cardiologists before the final report is issued.

Despite the fact that electrocardiography is one of the most important diagnostic tools at present available to clinical cardiologists, computerised electrocardiography still lacks recognition and has not achieved an essential place in clinical practice.

Computer sciences and the application of computer techniques have been helpful in providing more insight into many electrocardiographic problems. But in computerised electrocardiography emphasis has been placed on the computer rather than on electrocardiography: "Electrocardiography has been the proving ground for many of the basic concepts of medical decision making by computer".[1] Medical decision making by computer and clinical electrocardiography do not, however, necessarily have identical goals and should be carefully distinguished. At present computerised electrocardiography is still more an engineering project than a useful and applied diagnostic tool in clinical cardiology. Moreover, computerised electrocardiography has turned out to be not only the proving ground for medical decision making by computer, but also—and perhaps mainly—the playing field for the medical electronics industry. Our patients have served as testing objects for modern electrocardiographic equipment, often very sophisticated, but not very reliable in day-to-day use. This has all been at the expense of our patients and of our hospital budgets.[2] Clinical cardiologists shrug their shoulders over computer electrocardiography; let us briefly consider why this is so.

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State of art of electrocardiographic reading by computer

For the clinical evaluation of automated processing of electrocardiograms ambulatory patients are used rather than the critically ill.[3] Computer analysis of the electrocardiogram does not offer any help when the complexity of a particular electrocardiogram extends the intellectual skills of an experienced cardiologist.

For those patients with complex arrhythmias and/or complicated QRS patterns, computer diagnosis is not very helpful, a state of affairs which may not change within the next decade.[4] Up till now automated processing of electrocardiography has neither contributed to expertise in reading of clinical electrocardiograms nor to better understanding of the fundamental electrophysiological properties of the heart. In addition, computer analysis of the electrocardiogram is, in general, no more accurate than a trained electrocardiographer for routine reading of electrocardiograms of a hospital population.[5] In our experience it could not compete with respect to the cost or speed of reading of electrocardiograms, provided the human reader is provided with proper organisational tools, including support facilities.[6]

These unfavourable judgments, however, are only valid for those hospitals that have experienced and sophisticated facilities for reading electrocardiograms. There are undoubtedly many electrocardiographic services in smaller hospitals and remote places without highly skilled electrocardiographers to perform their routine readings of electrocardiograms. In those places computer electrocardiography may and probably does provide better and cheaper reading of electrocardiograms.[4]

Current clinical electrocardiography

All are aware of the contribution of electrocardiography to the diagnosis and treatment of all sorts of patients in clinical as well as in epidemiological studies, for men in outer space, for sports medicine, and other fields. Modern medicine would certainly suffer if electrocardiography were to be removed from it.

INADEQUATE STORAGE AND RETRIEVAL FACILITIES

Of all the electrocardiograms ever made probably more than 90 per cent are neatly folded and kept in an envelope in the private file of a doctor somewhere, somehow, or in the patients' data files of hospitals. In the same envelope or file the results of physical examinations as well as the outcome of laboratory tests, often illegible, can be found. The name of the patient, his initials, his date of birth, and the date the electrocardiogram was recorded may not have been noted on the electrocardiogram; in addition, the 1 mV calibration and the notation of the leads on the strip may be absent. Seldom is such an electrocardiogram of good technical quality, without artefacts, alternating current interference, or baseline drift caused by loosely fitted electrodes. Moreover, it is very difficult, if not impossible, to retrieve such electrocardiograms, for instance when needed for training purposes. An immeasurable amount of electrocardiographic data which could be useful for clinical or epidemiological cardiology is thus quite inaccessible and, to all intents, lost forever.

LACK OF STANDARDISATION

The worldwide application of electrocardiography is paradoxically matched by a total lack of uniformity in electrocardiography equipment and by a Babylonian confusion in electrocardiographic terminology, classification, and criteria. This causes a complete lack of any worldwide, national, or even local system for storage, retrieval, and analysis of electrocardiograms, and interferes with exchange of electrocardiographic data between doctors, hospitals, cities, and countries which is so vital for diagnosis and treatment of cardiac patients and important for epidemiological purposes.

Advantages of computer-assisted electrocardiography

Computerised electrocardiography, if it becomes a reliable and standardised method, can and will modify all these shortcomings, because computers require organisation and well-defined circumstances. Computerised electrocardiography will take care of storage, retrieval, and routine analysis of electrocardiograms. It will eliminate the recording and thus the storage of electrocardiograms of poor technical quality and of electrocardiograms without the necessary identification data of the patient. It will, one hopes, make electrocardiography technically as reliable in operation as a well-functioning telephone system. Computerised electrocardiography will force the user to organise himself to the great advantage of the patient whose electrocardiographic data will be of good technical quality and can be retrieved at will. This aspect of organisation seems to be the most important and most promising aspect of computer-assisted electrocardiography.

Why do we always emphasise the weakest aspect of computer electrocardiography—reading of electrocardiograms—while storage and retrieval barely receive any attention? Reading of electrocardiograms by computer will be helpful in handling large numbers of normal and well defined, easily recognisable abnormal electrocardiograms.[4] If reading of electrocardiograms by computer is not available or not desirable, an adequate electrocardiographic coding system can provide consistent terminology and classification which is a prerequisite for fast data retrieval.[7–9] So, even without computer analysis of the electrocardiogram, the computer can help to organise recording, storage, and retrieval of electrocardiograms. By using a coding system embedded in simple administrative computer processing, we were able inexpensively to reduce the electrocardiographer's time to avoid numerical errors and to improve standardisation of nomenclature.[6]

For computer interpretation of clinical electrocardiograms we have employed Pipberger's program.[10] On the basis of our experience it seems that if one considers different levels of complexity of electrocardiograms and present day limited program reliability reading of electrocardiograms by computer can and should be improved.

Future of computerised electrocardiography

STANDARDISATION OF TERMINOLOGY AND CRITERIA

At the tenth Bethesda conference on optimal electrocardiography a special task force was assigned to consider the quality of electrocardiographic recording. Definite requirements have been outlined for technician training, record format, lead nomenclature, electrocardiographic instrumentation, functional performance, standards for transmission of electrocardiograms, and computer acquisition and technical training criteria.[11] Thus the requirements for the hardware aspects of (computer-assisted) electrocardiography are well established for the future. However, only the first tentative steps have been taken by the World Health Organisation and the American College of Cardiology to reach an agreement on standardisation of terminology and interpretation.[12] What has been possible for aviation should be possible for electrocardiography as well. Standardisation of terminology is one of the cornerstones of present day worldwide air traffic facilities. Why not try to reach the same agreements for electrocardiography? A task force of the World Health Organisation has just published a report on definitions of terms related to cardiac rhythm[13] and a classification of cardiac arrhythmias which also may facilitate coding and analysis of electrocardiograms.[14] The QRS complex and ST-T segment, however, still remain *terra incognita* as far as any standardisation and/or definition of terms, let alone criteria, are concerned. Computerised electrocardiography certainly will force clinicians to reach agreement on criteria and nomenclature, but we still face a long road.

So, one major aspect of future development will be a worldwide accepted terminology for interpretation and coding of electrocardiograms.

ORGANISATION

In hospitals computer-assisted electrocardiography can be integrated into a total information system. This makes it possible to combine and correlate electrocardiographic data with other clinical information such as biochemical tests, *x*-ray reports, and the like. In addition, accounting facilities that can be linked with computerised electrocardiography may prove of importance for hospital administration.

The need for larger systems may be counterbalanced by the development and application of microprocessors which can be used in the electrocardiographic trolleys themselves. Besides signal control and signal improvement, unconfirmed reports will then be produced at the bedside, while overreading and storage of the electrocardiograms will take place in a large data base eventually connected with or integrated into a larger hospital information system. Non-routine electrocardiography like ambulatory and exercise electrocardiography will profit from specialised computer applications derived from standard processing of electrocardiograms such as data reduction capacity, indefatiguability, reproducibility, and computational power.

HIERARCHICAL ANALYSIS PROGRAM

There will always be electrocardiograms so difficult and complex that computer analysis is impossible. The same holds true for human reading. Every experienced electrocardiographer will admit that sometimes, if not often, electrocardiograms defy his skills.

So, if the future is to bring us fully integrated computer systems for handling the daily load of electrocardiograms we must face the fact that the development of one sophisticated program that is able to analyse all electrocardiograms without too many mistakes within a limited time period can be compared with the pursuit of a mirage. If we accept this axiom we should stop trying to develop programs which can handle every kind of electrocardiogram including the very complex and rare—the human brain is more suited for this. If computer reading of electrocardiograms should develop into a respected and useful clinical technique, one that can also help patients with complicated electrocardiographic abnormalities, we need a realistic approach based on clinical pragmatism rather than on wishful thinking. Such an approach could be the development of hierarchical programs. This would allow for more time and money for other important aspects of computer-assisted electrocardiography, such as storage and retrieval of the tracings and numerical data.

The first program should be used for electrocardiograms drawn from epidemiological studies, general practice, and small peripheral hospitals. From these sources we may expect a large number of normal electrocardiograms. Most available computer programs will handle these well.[3 4] The program itself should be able to identify the electrocardiograms of a level of complexity unsuitable for that program. The most important feature missing in present-day programs is a decision by the computer that its diagnostic statement about a particular electrocardiogram is unreliable or uncertain.

A second program should automatically be called into operation for more complex electrocardiograms or, for instance, for electrocardiograms coming from sources where as a rule abnormal electrocardiograms are being produced. This program should at least be able to diagnose the most common arrhythmias like normal sinus rhythm with premature complexes or atrial fibrillation or otherwise state: "undefined rhythm, for subsequent reading by a cardiologist". The program should further provide a reliable QRS-ST-T analysis, and again a warning statement should the program be unable to handle the electrocardiogram. If possible, it should provide facilities for comparison with previous electrocardiograms.

The third and most sophisticated program should handle the difficult electrocardiograms from patients in coronary and postsurgical intensive care units. These electrocardiograms usually defy conventional computer analysis. Thus a special program is needed which should also perform a sophisticated rhythm analysis.[15] For those electrocardiograms with the highest level of complexity which the third program cannot handle, a cardiologist is essential.

The future should therefore bring us three different programs each standing on top of the other, or a three-in-one package which, together with human assistance and reading, will provide expert reading of all electrocardiograms.

This approach will save computer time, computer memory, and last but not least, will employ the human mind for those problems it is most suited for, namely the unique ones. The present approach using one program for all electrocardiograms can be termed a failure, at least as far as its contribution to clinical cardiology is concerned.

References

1 Warner HR. First the electrocardiogram—then what? A system for decision-making by computer. *Am J Cardiol* 1978; **41:** 115–8.
2 Rautaharju PM. The impact of computers on electrocardiography. *Eur J Cardiol* 1978; **8:** 237–48.
3 Brohet CR, Richman HG. Clinical evaluation of automated processing of electrocardiograms by the Veterans' Administration Program (AVA 3.4). *Am J Cardiol* 1979; **43:** 1167–74.
4 Caceres CA. Limitations of the computer in electrocardiographic interpretation. *Am J Cardiol* 1976; **38:** 362–76.
5 Bourdillon PJ, Kilpatrick D. Clinicians, the Mount Sinai Program and the Veterans' Administration Program evaluated against clinico-pathological data derived independently of the electrocardiogram. *Eur J Cardiol* 1978; **8:** 395–412.
6 Meijler FL, Robles de Medina EO, Helder JC. An automated ECG system in a large hospital: coding, storage and retrieval of tracings. *G Ital Cardiol* 1975; **5:** 110–21.
7 Robles de Medina EO, Meijler FL. A simple numerical coding system for clinical electrocardigraphy. *Eur J Cardiol* 1974; **2:** 67–77.
8 Bonner RE, Caceres CA, Cuddy TE, *et al.* Recommendations for ECG diagnostic coding. Prepared by working group diagnostic codes. *Eur J Cardiol* 1978; **8:** 173–6.
9 Caceres CA. Electrocardiographic coding: an overview. *Eur J Cardiol* 1978; **8:** 145–53.
10 Pipberger HV. Computer analysis of the electrocardiogram. In: Stacy RW, Waxman B, eds. *Computers in biomedical research I.* New York and London: Academic Press, 1965: 377–406.
11 Tenth Bethesda Conference on optimal electrocardiography. Task Force II: Quality of electrocardiographic records. Sheffield LT (Chairman). *Am J Cardiol* 1978; **41:** 146–57.
12 Tenth Bethesda Conference on optimal electrocardiography. Task Force I. Standardization of terminology and interpretation. Surawicz B (Chairman). *Am J Cardiol* 1978; **41:** 130–45.
13 Bernard R, Coumel P, Damato AN, *et al.* Definition of terms related to cardiac rhythm. WHO/ISTC Task Force. *Am Heart J* 1978; **95:** 796–806.
14 Robles de Medina EO, Bernard R, Coumel P, *et al.* Classification of cardiac arrhythmias and conduction disturbances. WHO/ISFC Task Force. *Am Heart J* 1979; **98:** 263–7.
15 Plokker HWM. Cardiac rhythm diagnosis by digital computer. Thesis, Free University, Amsterdam, 1978.

Requests for reprints to Professor Frits L Meijler, Department of Cardiology, University Hospital, 3500 CG Utrecht, The Netherlands.

Br Heart J 1980; **44:** 5–13

Collateral arteries in pulmonary atresia with ventricular septal defect

A precarious blood supply

SHEILA G HAWORTH*

From the Department of Paediatric Cardiology, Institute of Child Health, Guilford Street, London

SUMMARY In pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries lung growth and survival depend on the size and continued patency of the collateral arteries. Arterial structure was examined in 13 collaterals, taken from the necropsy specimens of seven children, six of whom died during the first seven months of life. Serial reconstruction was made of two collaterals, from the aorta to the intrapulmonary vessels, and the other collaterals were examined by taking sections at intervals along the same course.

The collateral arteries arose from the aorta either as elastic vessels with a wide lumen or as muscular arteries when they were stenosed. Nearly all vessels rapidly came to resemble muscular systemic arteries, the external and lumen diameter becoming smaller. All collateral arteries save one showed areas of intimal proliferation which varied in the extent to which they surrounded and encroached on the lumen. In addition, four collaterals contained large intimal cushions which severely narrowed or even occluded the lumen. At the anastomosis of collateral and intrapulmonary artery intimal cushions were seen in all collaterals examined and the extent to which the structures reduced lumen diameter varied. The structure of collaterals is compared with that of growing systemic arteries and the ductus arteriosus, emphasis being given to the different types of intimal change. The clinical relevance of these findings is discussed.

The major aortopulmonary collateral arteries found in pulmonary atresia with ventricular septal defect either anastomose with a lobar pulmonary artery, with a segmental intrapulmonary artery or, less commonly, with a central pulmonary artery.[1] The segmental pulmonary arteries which anastomose with collateral arteries have no connection with the sixth arch or its branches within the lung. They do not differ either structurally or in their branching pattern from intrapulmonary arteries connected to central pulmonary arteries. Thus the term collateral artery refers only to the vessel connecting the aorta with the pulmonary segment.

Survival depends on the continued patency of the collateral arteries. In a large collateral some narrowing is desirable to reduce the systemic arterial pressure to a level more appropriate to the pulmonary circulation, but the degree of stenosis is critical because lung growth depends on the cross-sectional area of the collateral being adequate. Stenoses are seen radiologically and at necropsy, either as a localised constriction where the collateral arises from the aorta or where it anastomoses with a pulmonary artery, or as a narrowed segment. One collateral artery may be stenosed at several points.

Wall structure was examined in 13 collateral arteries, taken from seven published cases of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries.[1] The purpose of the present study was to assess the probability of collateral arteries remaining patent and growing as the child grows, the possibility of collateral arteries being able to constrict, and how their wall structure compared with that of systemic arteries and the ductus arteriosus. In addition, the structure of the collateral and large intrapulmonary arteries was considered in relation to the most suitable site for insertion of an aortopulmonary anastomosis or a right ventricular conduit.

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Materials and methods

Collateral arterial structure was studied microscopically in 13 arteries taken at random from seven cases of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. Serial reconstructions were made of two collaterals from the aorta to the intrapulmonary vessels, and the other collaterals were examined by taking sections at intervals along the same course (Table). The collaterals were always cut in transverse section, with the exception of one serial study in which a very tortuous artery was occasionally cut in longitudinal section. The sections were stained with Miller's elastic van Gieson stain and with a haematoxylin and eosin stain, except for the serial sections, all of which were stained with Miller's elastic van Gieson stain.

Emphasis was given to the following features: (1) the sequence of change in wall structure between the aorta and the lung, (2) the amount and distribution of elastic tissue and smooth muscle cells in the vessel wall, (3) intimal proliferation or cushions, and (4) splitting and fragmentation of the internal and external elastic laminae.

Results

Seven of the 13 collateral vessels arose from the aorta as relatively thin-walled elastic arteries with a large lumen (Table, Fig. 1). The remaining six collaterals were constricted, being thick-walled and muscular near their origin. All the collaterals save two had a predominantly muscular arterial wall structure throughout most of their course between aorta and lung, the remaining two vessels having a musculoelastic structure (Table). At the hilum of the lung 12 of the 13 collaterals connected with a segmental intrapulmonary artery and provided the only source of blood supply to those segments. As such a collateral artery approached a segmental bronchus it dilated and the wall became elastic in structure (Fig. 1). The remaining collateral anastomosed with a lower lobe branch of a centrally connected pulmonary artery which supplied an entire lung (Fig. 1). This collateral was thick-walled at the hilum and anastomosed with a thick-walled pulmonary artery.

Microscopically, the structure varied in each collateral artery along its course and in different collaterals, as shown by findings in two serial reconstructions.

SERIAL RECONSTRUCTION—CASE A

This collateral was not constricted at its origin from the aorta and the vessel wall was composed largely of long, unbroken elastic fibres (Fig. 2a). Gradually the elastic fibres became thinner and were separated by smooth muscle cells which occupied a progressively greater proportion of the

Table *Material, technique of examination, and summary of results*

Case	*Age*	*No. of collaterals*	*Technique of examination*	*Aortic origin*	*Muscular mid-portion*	*Collateral PA junction*	*Intra-pulmonary arterial structure*
A	12 days	1	Serial sections	Not narrowed	IP	IC	Normal
B	6 weeks	4	Step sections	Not narrowed	—	IC	Normal
			Step sections	Not narrowed	IP	?	Normal
			Step sections	Not narrowed	IP	?	Normal
			Step sections	Not narrowed	IP	?	Normal
C	3 months	2	Step sections	Narrowed	IP+	IC++	Normal
			Step sections	Narrowed	IP+++ IC	IC+++	Normal
D	4 months	1	Step sections	Narrowed	IP+++ IC Lumen obliterated	?	Normal
E	5 months	1	Serial sections	Not narrowed	IP+	IC	Normal
F	7 months	2	Step sections	Narrowed	IP+++	IC	Normal
			Step sections	Narrowed	IP++ IC	IC	Normal
G	3 years	2	Step sections	Narrowed	Musculoelastic IP	IC+++	Normal
			Step sections	Not narrowed	Musculoelastic IP IC	?	?

IP, intimal proliferation; IC, intimal cushion; ?, indicates structure not examined; PA, pulmonary artery; +, indicates size.

vessel wall as the collateral proceeded towards the lung. The subendothelial elastic fibres condensed into an internal elastic lamina, and short fine fragmented fibres lay in the intima. The external elastic lamina did not entirely surround the circumference of the vessel. The majority of elastic fibres merged into the adventitia. Thus, as the elastic lamellae disappeared a distinct media was formed and the elastic became a muscular artery. The external diameter decreased, and relative wall thickness increased.

In the distal half of the collateral eccentric areas of intimal proliferation were superimposed on an expanded media (Fig. 2b). In this region relative wall thickness increased to 23·4 per cent. Intimal proliferation did not entirely surround the lumen of the collateral at any point along its length and decreased as the collateral approached the hilum of the lung. Nearing the hilum, the proportion of elastic to muscular tissue increased and the vessel dilated. At this point approximately one-fifth of its circumference was covered by an intimal cushion which did not significantly narrow the lumen. Within the lung no intimal cushions were

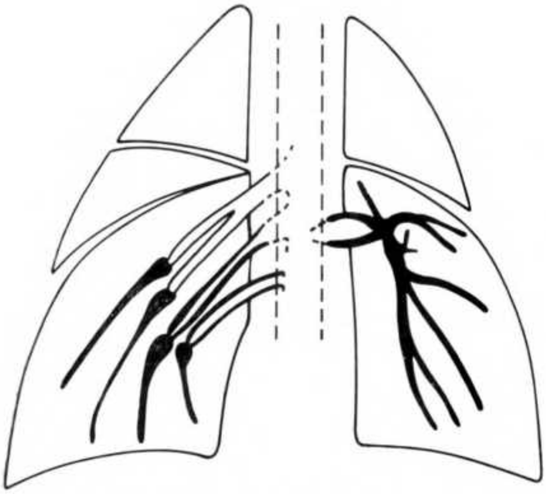


Fig. 1 *Diagram to illustrate the possible variation in collateral arterial structure showing, in the right lower lobe from above downwards, a branching collateral artery with a relatively large lumen, a collateral with a wide origin but thick muscular wall distally with intimal proliferation, and a collateral stenosed at its origin from the aorta. In the left lung a large collateral anastomosis with the lower lobe pulmonary artery. Solid lines indicate intrapulmonary arteries, the solid outlines indicate muscular walled collateral arteries, and the interrupted lines indicate the elastic portion of a collateral artery and the aorta.*

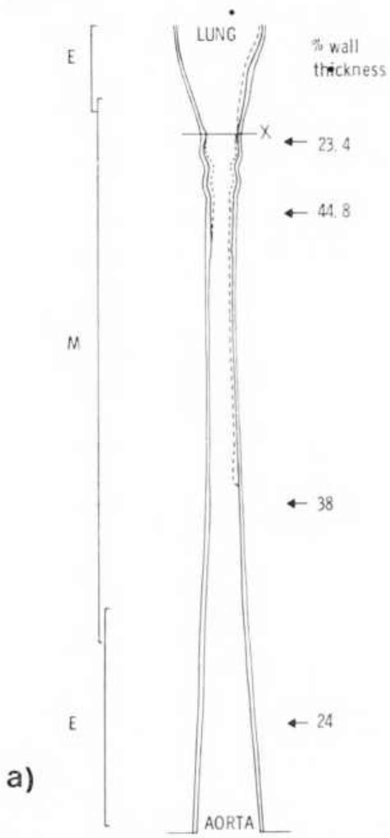
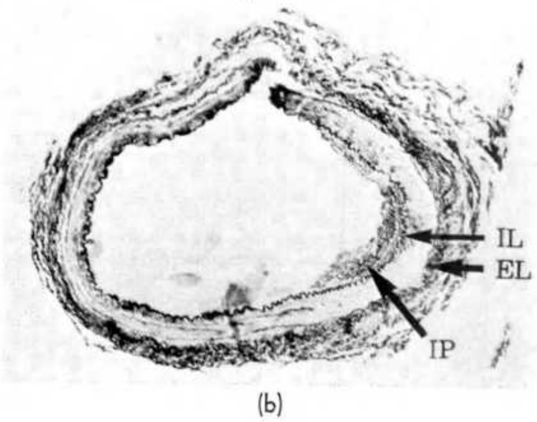


Fig. 2 (a) *Scale drawing of serial reconstruction—case A (magnification × 10) showing the reduction in external diameter in the muscular portion of the collateral which is exaggerated where intimal proliferation (------) is most pronounced. X = plane of section of Fig. 2b. Abbreviations: E, elastic wall; M, muscular wall.*
(b) *Transverse section of collateral artery, showing a muscular wall structure and an area of intimal proliferation (magnification × 45).*
Abbreviations: IL, internal elastic lamina; EL, external elastic lamina; IP, intimal proliferation.



seen and the vessel had a structure of a normally connected pulmonary artery.

SERIAL RECONSTRUCTION—CASE E

The structural features of this collateral are illustrated in Fig. 3. Intimal cushions were found at each branching point, becoming smaller with each successive division (Fig. 3c and d).

The small collateral destined to join the upper lobar pulmonary artery had a thick media with internal and external elastic laminae. Intimal proliferation covered approximately half the circumference and consisted of an inner layer of fine elastic fibres and an adluminal layer of relatively acellular amorphous material (Fig. 3d). The large parent collateral artery divided again. One vessel remained thick-walled, and in the other intimal cushions developed and beyond this the arterial wall became thin, the proportion of elastic fibres increasing in relation to the amount of smooth muscle. At this point the vessel became a segmental pulmonary artery of the left lower lobe (Fig. 3d).

ADDITIONAL FEATURES PRESENT IN THESE AND OTHER COLLATERAL ARTERIES

(1) *Aortic origin*

Six collateral arteries were narrowed at their aortic origin. At this point, all showed an extremely thick muscular media from which fleshy tongues of muscle encroached on the lumen (Fig. 4). Thick bundles of longitudinal muscle cells lay in the outer half of the media and circumferentially and obliquely orientated muscle cells lay beneath a reduplicated internal elastic lamina.

(2) *Mid section*

In the mid section of all save two collaterals the arterial wall changed from an elastic to a muscular structure approximately 1·5 to 2 cm from the aorta. External diameter decreased and relative wall

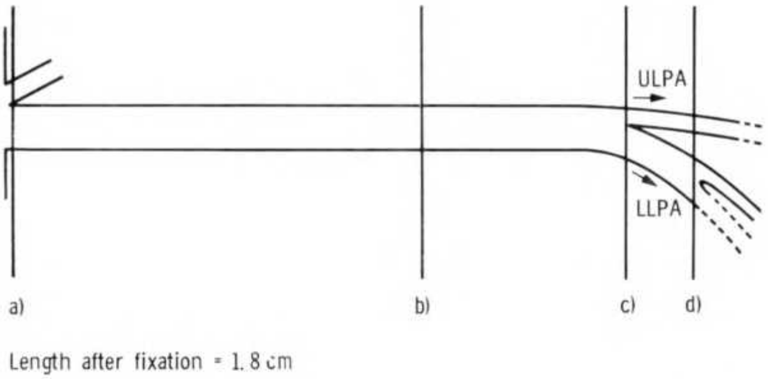
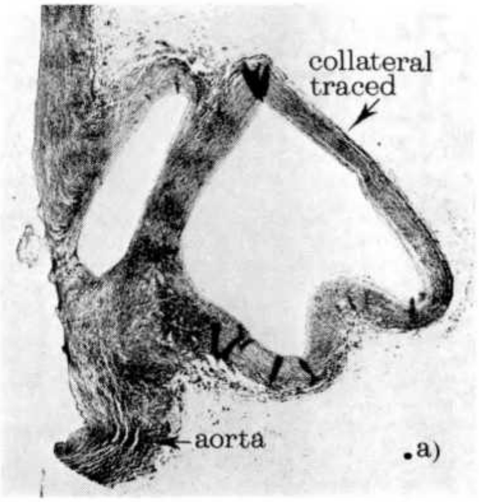
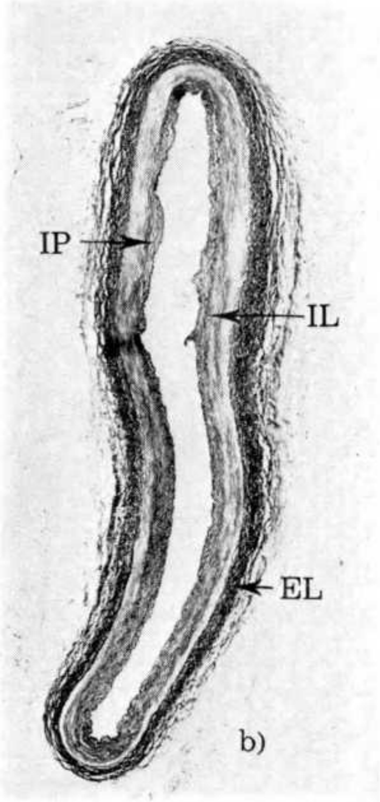
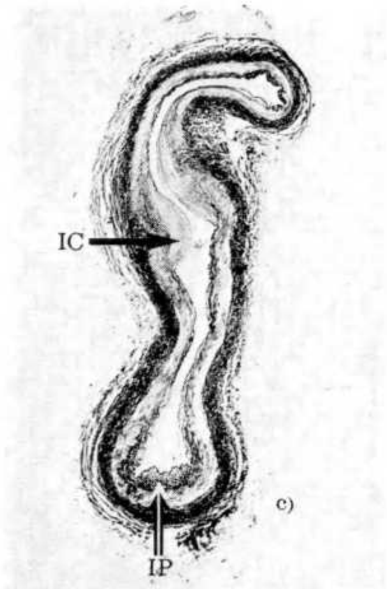
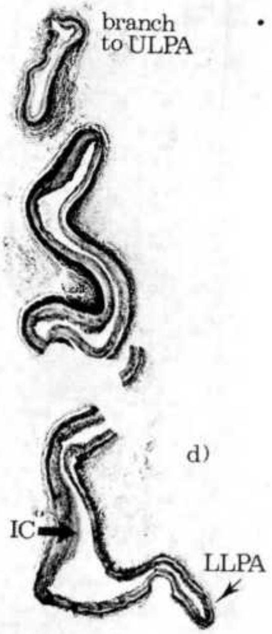


Fig. 3 *Serial reconstruction—case E. Line drawing of a collateral artery, from the aorta to where its branches join segmental intrapulmonary arteries. Photomicrographs* (a)–(d) *are sections taken at the points indicated on the diagram.*
(a) *collateral arising from the aorta (× 13·4), showing its elastic structure.* (b) *Muscular mid portion, showing thick media between internal and elastic laminae and intimal proliferation. Note variation in structure around circumference of vessel, particularly in amount of elastic material in media and intima (× 28).* (c) *Intimal cushions protrude into lumen at a branching point. Internal elastic lamina splits at edge of cushions (× 28).* (d) *Lowest branch of collateral joins segmental intrapulmonary artery, beyond intimal cushions (× 13). All sections stained with Miller's elastic stain. Abbreviations: ULPA, upper lobe pulmonary artery; LLPA, lower lobe pulmonary artery; IL, internal elastic lamina; EL, external elastic lamina; IP, intimal proliferation; IC, intimal cushion.*









thickness increased (Fig. 2, 3, 5, and 6), causing segmental narrowing in all instances, sometimes of a severe degree (Fig. 5 and 6).

The remaining two collateral arteries (case G) had a large lumen. Both had a musculoelastic wall structure. A broken external elastic lamina and a broken, frequently splitting internal elastic lamina bounded a media composed of smooth muscle cells

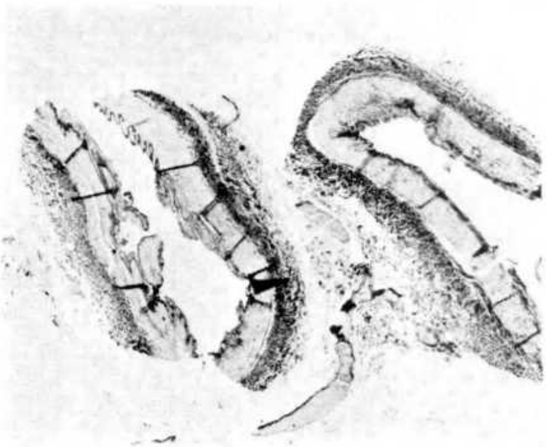


Fig. 4 *Transverse sections of a collateral narrowed at its aortic origin, showing a thick media, extensions of which project into the lumen (Miller's elastic stain × 29).*

interspersed with long, fine elastic fibres, forming 4 to 8 elastic laminae.

All the collateral arteries save one showed areas of intimal proliferation and, in four, intimal cushions projected into the lumen (Table).

(3) *Collateral-pulmonary artery anastomosis*
In all vessels in which the structure of the collateral-pulmonary artery anastomosis was examined, near or within the hilum of the lung intimal cushions projected into the lumen, reducing its cross-sectional area (Fig. 3d). In three collaterals, large cushions were covered by a thick layer of amorphous material. Beyond this point the muscular wall gradually became elastic, until within the lung parenchyma the wall structure was that of an elastic pulmonary artery (Fig. 7). The pulmonary arteries were dilated where they connected with a collateral artery, occasionally producing a sinusoidal cavity from which arose abnormally small segmental arteries.

Irrespective of the severity of luminal narrowing produced by the intimal mounds, the distal pulmonary arteries were invariably patent.

STRUCTURE OF INTIMAL CUSHIONS
The type of intimal change varied along the course of each collateral and also in the same region of different collaterals. In the muscular mid-section two types of intimal change occurred, either small areas of intimal proliferation or large intimal cushions. Small areas of proliferation were present in nearly all cases, even at 12 days of age (Fig. 2b). They varied in size, but did not cause significant narrowing of the lumen. By contrast, large intimal cushions occurred in only four collaterals, but in all they narrowed or even obliterated the lumen (Fig. 5 and 6). At the margin of all areas of intimal proliferation and cushion formation, the dense internal elastic lamina usually split, a larger proportion continuing as a broken internal elastic lamina, the adluminal part splitting into fine fragmented fibres lying within the expanded intima.

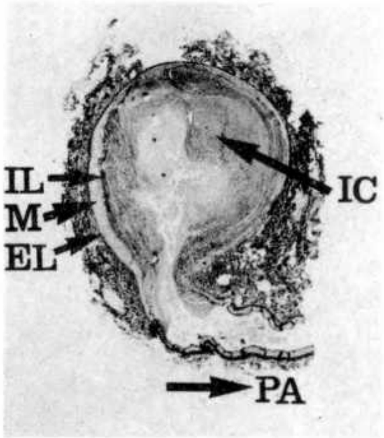


Fig. 5 *Transverse section of the mid portion of a collateral at a region of segmental narrowing. The lumen of this muscular artery is almost totally obliterated by intimal proliferation and cushion formation, and a layer of amorphous material containing no elastic tissue (Miller's elastic stain × 17).*
Abbreviations: IL, internal elastic lamina; EL, external elastic lamina; M, media; IC, intimal cushion; PA, pulmonary artery.

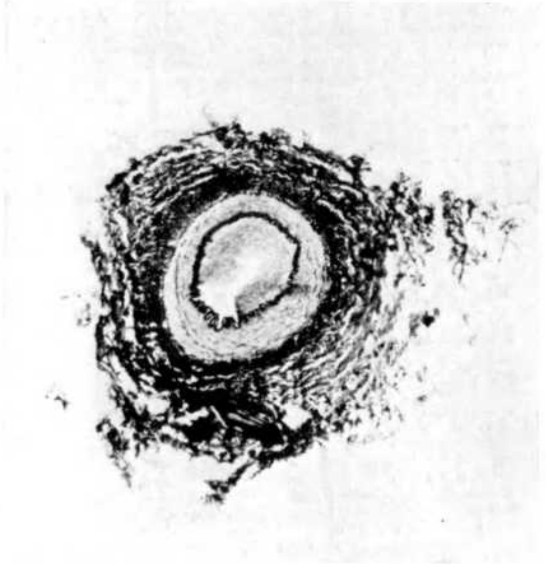


Fig. 6 *Transverse section of the mid portion of a collateral at a region of segmental narrowing, showing a thick media and narrowing of the lumen by intimal proliferation and mound formation. Intimal mounds contain fine elastic fibres and are covered with a layer of acellular material (Miller's elastic stain × 38).*

The cushions contained many collagen fibres. Towards the lumen of the vessel the cushions became progressively less cellular, contained fewer elastin and collagen fibres, and were frequently covered by amorphous and relatively acellular material. No subendothelial elastic lamina was present. Beneath the cushion the smooth muscle of the media was often thinned and the cells were no longer arranged in a regular concentric manner, but ran in an oblique, irregular fashion between broken internal and external elastic laminae (Fig. 5). Bundles of longitudinal muscle fibres frequently lay on either side of the internal elastic lamina. The number of elastic fibres usually increased considerably in relation to the amount of smooth muscle.

In three of the four collateral arteries containing large cushions the outer third of the media showed hyaline change, and at this point the lumen was entirely surrounded by intimal proliferation and cushion formation.

At the branching point of a collateral artery the intimal cushions were more clearly defined structures than those described above (Fig. 3c). They consisted of long thin branching elastic fibres, generally running circumferentially around the lumen. They did not have a thick subendothelial elastic lamina, and were not covered by layers of amorphous material. The intimal cushions present at the junction of a collateral and a segmental pulmonary artery were smaller than those found at the branching points, but had a similar discrete appearance (Fig. 3d). In this position, occasionally a thick layer of intimal proliferation, sometimes with a layer of amorphous material, was superimposed on a well-defined intimal cushion.

Discussion

Findings in the present study help to explain the radiological appearances of the collateral arteries during life. As they arose from the aorta some vessels generally had an elastic wall structure and a wide lumen, but others were constricted at their origin because of a thick muscle wall. The external and lumen diameter of the collaterals narrowed as the elastic vessels came to resemble muscular systemic arteries. Four vessels contained an extremely narrow segment composed of a thick muscle wall with intimal proliferation and cushion formation. At the anastomosis of a collateral with a pulmonary artery intimal cushions were seen in all the collaterals examined, but the extent to which these structures reduced the lumen diameter varied. Distally the pulmonary artery was large, irrespective of the severity of stenosis, and sometimes showed post-stenotic dilatation.

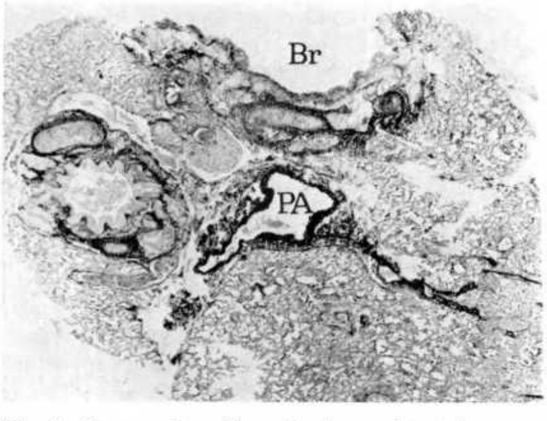


Fig. 7 *Cross-section of lung showing an intrapulmonary artery which was connected proximally to a collateral artery. The vessel has the elastic wall structure of a typical pulmonary artery (Miller's elastic stain × 21). Abbreviations: Br, bronchus; PA, pulmonary artery.*

In pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries, survival depends on the collateral arteries. Intimal proliferation and cushion formation was found in the majority of collaterals examined and in several the lumen was almost or totally occluded. Not all the intimal change, however, was necessarily pathological. The small areas of intimal proliferation found in the muscular mid-section of the collaterals were structurally similar to those described by Robertson[2] in the brachial, popliteal, and coronary arteries of the fetus and by Dock,[3] in the coronary arteries of the newborn. Robertson[2 4] did not regard these fetal cushions as pathological. The normal development of intimal pads in systemic arteries might explain their presence in the collateral arteries of young infants. In systemic arteries, the function of intimal pads is not understood, but they may represent growing points and might also strengthen the vessel wall. Pulsatile stress is thought to stimulate cushion formation, stimulating longitudinal orientation of medial muscle and the formation of muscle in the intima.[2 4] Collateral arteries are, of course, subject to the pulsatile stress of the thoracic aorta.

As in the present study, intimal cushions or pads have been described at the branching points of brachial, popliteal, and cerebral arteries in the fetus and are thought to have a supportive function.[2 4 5] They have not been described in the fetal and newborn lung (A Hislop, 1980, personal communication), but in the adult they are present at the mouths of lateral branches arising from the segmental axial artery.[6]

Intimal cushions were also present at the site of anastomosis between a collateral and intrapulmonary artery, the site at which these vessels are probably normally connected in early fetal life and then, presumably, in the normal fetus, are later disconnected when the intrapulmonary arteries become exclusively connected to the sixth arch. In this position, the intimal cushions were frequently covered by a thick layer of intimal proliferation and a superficial relatively structureless layer. This appearance suggests that superimposed on discrete intimal cushions, layers of intimal proliferation caused progressive narrowing of the vessel lumen.

It may be that intimal pads develop *in utero* in collateral and in normal arteries, and in both are the site of early obliterative change.[3 4] The intimal cushions present in the muscular mid-section of several collaterals were larger than those previously discussed and less discrete. In some collaterals remnants of intimal cushions could be seen beneath a less structured layer of intimal proliferation containing relatively little elastic material. The basic structure of collateral arteries may predispose them to obliterative change. The collateral arteries described in the present study had a thick muscular wall, whereas large conducting arteries so close to the thoracic aorta normally have a predominantly elastic wall structure. The muscular collateral arteries are presumably less distensible and are also capable of contracting in response to a high distending pressure. When the lumen is narrowed the velocity of flow increases, increasing the shearing stress on the endothelium and the likelihood of producing intimal damage and proliferative change.[7]

The structure of the narrowed collateral arteries resembled that of a normally closing ductus arteriosus.[8] Like the ductus, the collaterals resembled muscular systemic arteries and several contained intimal cushions structurally similar to ductal cushions. Like the normally closing ductus arteriosus, no subendothelial elastic lamina was present. In both collateral arteries and the ductus arteriosus areas of cytolytic necrosis and mucoid lakes occurred in the inner media and base of the intimal cushions. These similarities may indicate only that the structural mechanism by which these muscular arteries, or indeed any muscular artery, are obliterated is similar, irrespective of the functional stimulus which provokes the change. Alternatively, the structural similarities between the narrowed collateral arteries and closing ductus arteriosus and the propensity for both channels to close in early postnatal life may imply that both structures are persistent fetal channels which are destined to close. Boyden[9] suggested that collateral arteries are persistent segmental arteries which normally close about 50 days after ovulation. We might therefore be witnessing delayed "normal" closure of segmental arteries in infants with pulmonary atresia and ventricular septal defect. This could explain why severe obliterative change was found in such young infants. A high transmural pressure alone might not be sufficient to produce such severe obliterative change so rapidly.

Clearly, not all collateral arteries become severely narrowed because some children with pulmonary atresia, ventricular septal defect, and major aortopulmonary collateral arteries reach adolescence. There is evidence to suggest that the variable natural history might be a result of a basic structural difference in the collateral arteries. In the present study two thin-walled collateral arteries present in the 3-year-old child contained a greater amount of elastic tissue than did the collaterals of the younger cases. Two large collateral arteries in a 7-year-old child, not included in the present series, had a wall composed of densely packed elastic laminae. In these four collaterals, intimal change was less frequent and less severe than in the muscular collateral arteries and though the midsection of one collateral contained a large intimal cushion this did not produce significant narrowing of the wide lumen.

The difference between the wall structure of collaterals with a relatively large lumen found in older children and that in the majority of collateral arteries in the infant group is similar to that between the persistently patent and normally closing ductus arteriosus. A persistent ductus arteriosus usually contains more elastic tissue than a normally closing ductus, sometimes showing lamella formation.[8] A patent ductus is, however, characterised by a wavy unfragmented subendothelial elastic lamina which continues as a thick fibre on top of the cushions, while in the collateral arteries this elastic lamina became fragmented within the cushions.

These observations suggest that collateral arteries containing a greater proportion of elastic rather than smooth muscle tissue are larger and remain patent for a longer period of time than do muscular collateral arteries. It is also possible that an increase in elastin is secondary to prolonged patency. In the ductus arteriosus, however, there was no relation between age and the occurrence of a subendothelial lamina and the amount of elastic material in the ductus wall.[8] Further studies of collateral arterial structure in older patients are obviously necessary.

CLINICAL IMPLICATIONS

The question arises as to whether any pharmacological agent might encourage the collateral arteries to remain patent. Prostaglandin E_1 dilates the normally closing ductus, but a structural similarity between the closing ductus and a closing collateral artery does not necessarily imply a functional similarity. Moreover, to be effective prostaglandins would have to be given prophylactically from birth since once fibrous obliterative change is present and the media is thinned the vessel is unlikely to respond to any vasodilator drug.

A necropsy study obviously gives a biased impression of the natural history of any condition. Findings in the present study, however, indicate that in young infants with pulmonary atresia, ventricular septal defect, and major aortopulmonary collateral arteries, the collateral arteries can undergo obliterative change, and are unlikely to increase in size as the child grows. These observations help explain why infants with this anomaly frequently become increasingly cyanosed during the first months of life. Furthermore, quantitative morphometric analysis of areas of lung periphery perfused by the collateral arteries described in the present series, showed impaired lung growth, usually because of hypoperfusion.[1] Because large occlusive intimal cushions can develop at the junction of collateral and intrapulmonary arteries, an aortopulmonary anastomosis or a right ventricular conduit should be inserted beyond the collateral artery, at the origin of the intrapulmonary vessel.

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References

1 Haworth SG, Macartney FJ. Growth and development of pulmonary circulation in pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. *Br Heart J* 1980; **44:** 14–24.

2 Robertson JH. Stress zones in foetal arteries. *J Clin Pathol* 1960; **13:** 133–9.

3 Dock W. The predilection of atherosclerosis for the coronary arteries. *JAMA* 1946; **131:** 875–8.

4 Robertson JH. The influence of mechanical factors on the structure of the peripheral arteries and the localization of atherosclerosis. *J Clin Pathol* 1960; **13:** 199–204.

5 Stebhens WE. Focal intimal proliferation in the cerebral arteries. *Am J Pathol* 1960; **36:** 289–302.

6 Elliott FM. The pulmonary artery system in normal and diseased lungs—structure in relation to pattern of branching. University of London: PhD Thesis, 1964: 261–71.

7 Fry DL. Acute vascular endothelial changes associated with increased blood velocity gradients. *Circ Res* 1968; **22:** 165–97.

8 Gittenberger-de Groot AC. Persistent ductus arteriosus: most probably a primary congenital malformation. *Br Heart J* 1977; **39:** 610–8.

9 Boyden EA. The time lag in the development of bronchial arteries. *Anat Rec* 1970; **166:** 611–4.

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Br Heart J 1980; **44**: 14–24

Growth and development of pulmonary circulation in pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries

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SUMMARY In 11 necropsy specimens of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries, central pulmonary arteries were present in all cases, supplied by collateral arteries which anastomosed with a lobar pulmonary artery or, less commonly, with a central pulmonary artery. These normally connected pulmonary arteries frequently perfused only a minority of bronchopulmonary segments. The remaining segments were connected to collateral arteries which, within the lung, were continuous with vessels which had the structure of normally connected vessels and branched with the pre- and intra-acinar airways in a normal manner to perfuse the alveolar capillary bed. These collateral arteries and the intrapulmonary vessels with which they anastomosed had no connection, either macroscopically or microscopically, with either the central pulmonary arteries or their branches within the lung. Irrespective of the type of proximal connection, the segmental pulmonary arteries were generally abnormally small. Stenoses occurred in 58·8 per cent of collateral arteries, usually as a thick-walled narrowed muscular section between the aorta and lung. Microscopically, quantitative morphometric analysis showed that within the respiratory unit the pulmonary circulation had failed to grow normally in all save the youngest patient dying at 12 days of age. The structural changes were usually consistent with a reduction in pulmonary blood flow; only three cases contained any segments of lung showing structural evidence of pulmonary hypertension. These anatomical and histological findings are discussed in relation to the embryology, nomenclature, and natural history of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. The structural findings provide a rational basis for the clinical management of this condition.

The preoperative assessment of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries has been improved by selective catheterisation of the collateral arteries. Corrective surgery is now possible using valve-bearing conduits to establish continuity between the right ventricle and pulmonary circulation. The management of this condition remains imperfect, however, mainly because the anatomy of the pulmonary circulation is poorly understood. Radiological, haemodynamic, and surgical studies often provide an incomplete picture of the source of pulmonary blood supply and the intrapulmonary arterial branching pattern. In addition, the structure of the pulmonary circulation at alveolar level determines pulmonary vascular resistance and hence prognosis, but its growth and development has not previously been studied in this condition.

In an attempt to provide a rational basis for treatment, the central pulmonary arteries and collateral arteries were traced from their origin to the lung periphery in 11 necropsy specimens. Peripheral lung structure was analysed using quantitative morphometric techniques.

Subjects and methods

The lungs of 11 patients who died between 1950 and 1978 were studied (Table 1). Cyanosis was noted within the first two days in four babies, within the first two months in a further four, at 5 months in case 7, and at 2 years in the remaining documented case (one case was undocumented). Nine children underwent cardiac catheterisation.

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Table 1

Case no.	*Age at death*	*Sex*	*No. of collaterals to each lung*		*Destination of collaterals*		*No. bronchopulmonary segments connected to central PA*	
			Right	*Left*	*Right*	*Left*	*Right*	*Left*
1	12 days	M	2	1	RPA+P	P	3	2
2	15 days	M	2	2	P	ULPA+P	8	3
3	1 month	F	2	1	P	LPA	6	9
4	1·5 months	M	3	3	ULPA+P	P	3	0
5	3 months	M	2	1	P	LLPA	4	9
6	4 months	F	3	2	P	ULPA+P	1	3
7	5 months	M	4	1	ULPA+P	P	1	3
8	5 months	F	3	0	LLPA+P	—	4	9
9	5 months	F	3	2	P	LLPA+P	6	3
10	7 months	F	2	3	ULPA+P	P	8	0
11	3 years	M	3	3	ULPA+P	LLPA+P	5	3

PA, pulmonary artery; ULPA, upper lobe pulmonary artery; LLPA, lower lobe pulmonary artery; P, parenchyma supplied by collaterals not connected to central pulmonary arteries or their branches.

Central pulmonary arteries were demonstrated in six patients, but selective angiography of the collateral arteries was performed in only three patients, those admitted after 1976. Central pulmonary arteries were shown in all patients in whom selective injections were performed. Five patients did not receive surgical treatment. Three others died at or immediately after operation and are included in the untreated group. In the remaining three patients, an aortopulmonary anastomosis increased pulmonary blood flow in cases 4 and 8, but an aortocollateral anastomosis did not increase flow in case 6.

PATHOLOGICAL TECHNIQUES

The diagnosis was confirmed at necropsy in all cases. Atrial situs was normal. In nine cases the lungs had been fixed in formalin, uninflated, for routine pathological study. In the other two specimens the pulmonary arterial circulation was injected with a "Micropaque" gelatin mixture and the lungs were fixed by inflating the airways with formol saline.[1 2] In all 11 cases the bronchial branching pattern was traced from the hilum to segmental level and compared with the normal pattern.[3] By dissection, the course of each pulmonary artery and collateral artery arising from the aorta was mapped out on a diagram illustrating the normal bronchial branching pattern (Fig. 1 and 2). The external diameter of all arteries was measured at intervals along the pathways. The collateral arteries, central pulmonary arteries, and all arteries within the lung down to subsegmental level were examined for localised stenoses and segmental narrowing. Because most of the specimens were small and fixed, the bronchial arteries (those vessels arising from the plexus around the lower end of the trachea and carina, and running along the wall of the bronchi) could only be identified with certainty in eight cases. Radiographs were taken of the two injected specimens.

Microscopical studies

In the two injected specimens, after tracing the intrapulmonary arterial branching pattern as far as possible macroscopically, blocks of tissue which contained vessels connecting with collateral arteries were serially sectioned. These vessels were then traced to the alveolar wall. In order to study peripheral pulmonary vascular structure, lung tissue was taken from the two injected and seven uninjected specimens. This gave a total of 33 blocks, in each of which the origin of the blood supply to the block had been traced macroscopically. Applying quantitative morphometric techniques, the muscularity, size, and number of intra-acinar* arteries was determined and the findings were compared with those in age-matched controls.[4 5] In each case both injected and uninjected, percentage arterial wall thickness was calculated in a large proportion of vessels, for example 280 vessels in case 4. In arteries cut transversely, the external diameter of an artery was measured across two diameters by taking the distance between external elastic laminae; wall thickness was measured from external to internal elastic lamina at the four sites where the measured diameters cut the wall and the mean of the four readings was used. The percentage medial wall thickness was then calculated as:

$$\frac{2 \times \text{wall thickness}}{\text{external diameter}} \times 100$$

In addition, in both injected and uninjected tissue extension of muscle into the acinus was determined. In the injected tissue, the external diameter of arteries accompanying terminal and respiratory bronchioli, alveolar ducts, and alveolar walls was

* An acinus is all the lung tissue distal to a terminal bronchiolus.

estimated, while in the uninjected tissue only the size of arteries accompanying the respiratory bronchioli, the most easily and accurately identifiable of the peripheral airways, was measured. Only in the injected specimens was the number of alveoli and arteries per unit area of lung, expressed as a ratio, obtained for each block of tissue.

Out of a total of 48 collateral arteries, transverse sections of 13 vessels were examined at their origin from the aorta, midway along their course, and where the collateral artery first came to lie adjacent to a main, lobar or segmental bronchus.

All the sections were stained with haematoxylin and eosin, and with Miller's elastic van Gieson stain.

Results

In all cases, the bronchial branching pattern was normal, central pulmonary arteries were present, and pulmonary venous return was normal. A right aortic arch was present in three cases.

ORIGIN OF COLLATERAL ARTERIES FROM AORTA

In each case either two or three collateral arteries arose in close proximity from the descending thoracic aorta, at the inferior margin of the left main brochus in the presence of a left aortic arch and immediately below and to the right of the carina in the presence of a right arch. Five collateral arteries branched 1 to 2 cm from their origin. Ultimately, a total of 39 collaterals from the descending aorta entered the lungs studied (Table 1). An additional six collaterals arose underneath the aortic arch. A further three vessels arose from a small artery running down the lateral margin of the trachea, whose origin could not be traced. Thus a total of 48 collateral arteries entered the lungs studied, the majority of which arose from the descending thoracic aorta.

PULMONARY ARTERIAL BRANCHING PATTERN

In any one case, a collateral artery might anastomose with either a central pulmonary artery, or a normally connected lobar pulmonary artery, or else enter the lung parenchyma and appear to branch within it, having no connection either with the central pulmonary arteries or with the vessels arising from them within the lung. All cases had more than one type of arterial connection and these could be found in any combination (Table 1, Fig. 1 and 2).

Collateral arteries destined to join an upper lobe pulmonary artery ran posterior to the main bronchus, anastomosing at its superior margin with

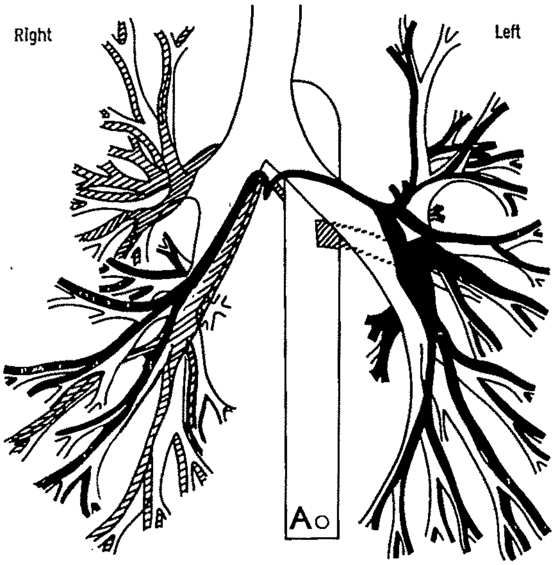

Fig. 1 *Pulmonary arterial branching pattern in case 5. The solid lines indicate the central pulmonary arteries and their branches, and the cross-hatched lines indicate collateral arteries and the intrapulmonary arteries with which they connect. In the right lung, the central pulmonary arteries only connect with the middle lobe and two segments of the lower lobe. Ao, aorta.*

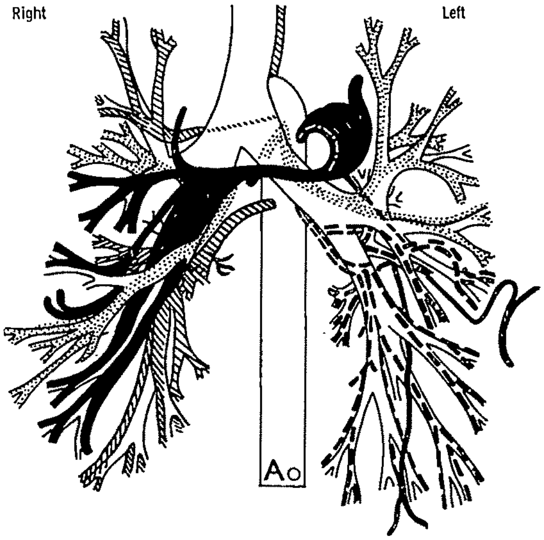

Fig. 2 *Pulmonary arterial branching pattern in case 4. The solid lines indicate the central pulmonary arteries and their branches, and the cross-hatched, stippled, interrupted, and dotted lines, the collateral arteries and the intrapulmonary arteries with which they connect. Ao, aorta.*

the centrally connected pulmonary artery. Collaterals to a lower lobe pulmonary artery ran posterior to the lower lobe bronchus, anastomosing at its lateral margin. Of the collateral arteries not connecting with the central or lobar pulmonary arteries, those vessels supplying segments of the upper and lower lobe usually ran posterior to the appropriate bronchus, save those to the anterior basal segment of both lower lobes and the median basal segment of the right lower lobe, which ran along the inferior margin of the main or lower lobe bronchi before entering the lung. On entering the lung, all these vessels ran towards the nearest lobar or segmental airway, coming to lie in the normal position of a "true" normally connected pulmonary artery, anterolateral to the airway. Macroscopical dissection, until at least one division beyond segmental level, showed that these vessels branched with the airways (Fig. 1 and 2). Microscopically, in the serial sections of injected material the intrapulmonary vessels which connected to each segmental artery continued to branch with the airways, the small bronchioli, terminal and respiratory bronchioli, and alveolar ducts until they reached the capillary bed of the alveolar wall.

Considering the group as a whole, the central pulmonary arteries were only connected to 93/209 bronchopulmonary segments whereas the collateral arteries were the only arteries connected to a further 91/209. In an additional 19 segments both centrally connected and collateral arteries accompanied lobar and segmental airways, but further along the pathway the arteries diverged, each accompanying a different airway to supply a different portion of the bronchopulmonary segment. The remaining six segments were perfused by an artery running alongside the trachea. Five of these segments were within an upper lobe and the remaining segment within a middle lobe.

The bronchial arteries entered four lobes which were perfused by collateral arteries. The remaining identified bronchial arteries perfused regions of lung connected to central pulmonary arteries. Enlargement of the bronchial arteries occurred in two cases, involving three lobes where the central pulmonary arteries were extremely small. In one injected case (case 4), a collateral artery arising from underneath the aortic arch gave rise to a small branch which ran into the wall of the right lower lobe posterobasal bronchus.

Dissection and tracing of all arteries entering the lung failed to show any macroscopical connections distal to the lobar bronchi between arteries connected to the central pulmonary arteries and those arising from the aorta. On microscopical examination of all lung sections, including the serial sections, no anastomoses were seen between peripheral pulmonary arteries connected to central and collateral arteries.

SIZE OF PULMONARY ARTERIES

The main, right, and left pulmonary arteries were extremely small, but were patent in all except case 8 (Table 2). The central pulmonary arteries were particularly small where they had been perfused by retrograde flow from a collateral vessel which anastomosed with the lower lobe artery (cases 5, 8, and 9). Within the lung the arteries were usually abnormally small, whatever the type of proximal connection (Table 2). In the right lower lobe, for example, an approximately equal number of segments were connected to collateral and central pulmonary arteries in 8/11 cases. Nearly all the lower lobe arteries were small in relation to the size of the airway, 12 measuring less than 3 mm in diameter. In the three remaining specimens all the segments of the right lower lobe were supplied by a single artery and even then, in two instances, the vessel measured only 2·5 mm in diameter. In five specimens the arteries connected to a collateral vessel were larger than those connected to the central pulmonary artery (Table 2).

The effect of an aortopulmonary anastomosis in an individual patient cannot obviously be judged from a study of postmortem material. Arterial size was not, however, noticeably greater in treated than in untreated specimens. After an aortocollateral anastomosis (case 6), the intrapulmonary artery connected to the collateral remained small, measuring 2 mm.

The pulmonary arteries, though small, had a normal appearance, save in cases 9 and 12, where the normally connected left and right upper lobe

Table 2 *Pulmonary arterial size: external diameter (mm)*

Case no.	*Central pulmonary arteries*		*Intrapulmonary arteries of right lower lobe, connected to*	
	Right	*Left*	*Pulmonary valve*	*Aorta*
1	3	2·5	2·5	2·8
2	5	4	1·5	2·3
3	5	5	4	2·5
4*	4·2 (APA)	3	4	3
5	2·8	2·8	2·8	2
6	Pp (APA)	Pp	1·5	3·5
7	2·5	2·5	—	2·5
8	Not pp	Not pp	2·2	6·5
9	2·3	2	2·5	—
10	4·5	4·5	7·5	—
11*	8	7	5·1	2·8

All measurements made on fixed material.
* Arteries distended by injection.
APA, aortopulmonary anastomosis; pp, probe patent.

pulmonary arteries, respectively, were dilated and saccular at lobar and segmental level.

STENOSES

Dissection of the *uninjected* specimens showed at least one site of narrowing in 20/36 collateral arteries. A narrowed segment between the aorta and the lung was the commonest site of stenosis, present in 15 collaterals. A localised constriction occurred at the aortic origin of four collaterals and at the anastomosis of a collateral with the normally connected extrapulmonary or lobar pulmonary artery in four of the nine cases with this type of connection. In the two *injected* specimens, macroscopical and radiological examination of the 12 collateral arteries present demonstrated five examples of segmental narrowing of a collateral artery, two examples of a localised stenosis of a collateral at its aortic origin, and two of narrowing at the anastomosis of a collateral with a lobar pulmonary artery. Radiologically, no stenoses were seen at segmental level or beyond.

In all cases, when a collateral reached a bronchus either at the hilum or within the lung, the vessel increased considerably in size and became thin walled immediately before it branched with the airways and followed the course of a normally connected pulmonary artery.

MICROSCOPICAL STUDIES

In all cases, when a collateral artery arose from the aorta the wall structure resembled that of a muscular systemic artery. Within the lung, all the collaterals examined connected with vessels which had the structure of a normal pulmonary artery with a thin media containing six to eight elastic laminae between internal and external elastic laminae. The detailed histological studies of collateral arterial structure are presented elsewhere.[6]

Within the lung, in all cases the alveolar walls appeared normal, but the thickness of connective tissue septa was frequently increased.

Arterial wall structure

Percentage medial thickness was similar in segments of lung perfused by centrally connected pulmonary arteries and by collaterals in the five cases in which the comparison was made, and was either normal or reduced (Fig. 3). Examination of the structure of arteries accompanying peripheral airways showed that muscle extended as far along the arterial pathway as is normal for age, save in the oldest child, case 11, where muscle failed to extend as far along the pathway as normal. In three cases, a total of four segments contained vessels showing eccentric intimal change which encroached little on the arterial lumen. These findings are usually associated with a low pulmonary blood flow. In the older 3-year-old child, many small preacinar arteries and arteries accompanying terminal and respiratory bronchioli in the median basal segment of the right lung showed concentric intimal fibrosis, with partial or complete obliteration of the lumen. In this segment of lung, postmortem arteriography showed a reduction in density of the background haze, suggesting a reduction in number of intra-acinar arteries.[7]

Of the remaining three cases in which no comparison was made between segments perfused by collateral and centrally connected pulmonary arteries, each contained at least one segment showing the medial hypertrophy and abnormal extension of muscle along the arterial pathway associated with pulmonary hypertension. Two segments were connected to a centrally connected pulmonary artery fed by a large collateral vessel, and one to a large collateral artery. Only two segments showed, in addition to medial hypertrophy, concentric intimal proliferation. One segment was perfused by a Blalock-Taussig shunt

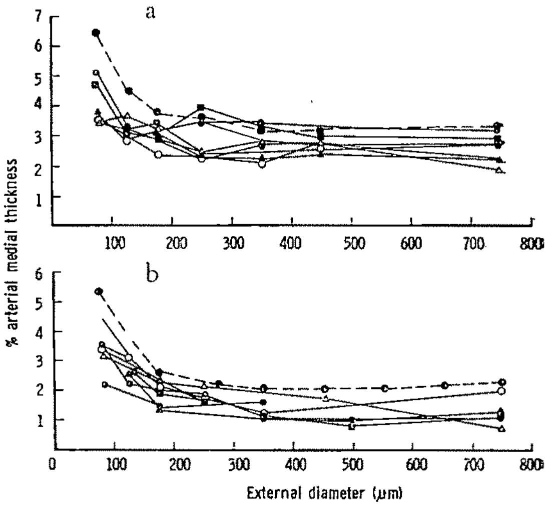

Fig. 3 *Pulmonary arterial medial thickness related to external diameter (µm); (a) case 4, aged 1·5 months, illustrating muscularity in three bronchopulmonary segments of the right and four segments of the left lung* (solid lines), *compared with normal* (interrupted line); (b) *case 11, aged 3 years, illustrating muscularity in five segments of the right and two segments of the left lung* (solid lines), *compared with normal of similar age* (interrupted line). *In each case, muscularity is generally below normal and similar in different segments of lung, each segment being perfused by a different vessel.*

and the other by a large collateral perfusing only two segments of lung.

Thus, in a majority of cases the microscopical findings in all sections of lung examined were compatible with a reduction in pulmonary blood flow. In only three cases was there structural evidence of pulmonary hypertension.

Peripheral arterial size

Arterial size varied between and within cases. In five cases, the arteries accompanying respiratory bronchioli were abnormally small in some or all of the segments examined. In the four remaining cases arterial size was normal in all segments examined.

In general, the size of arteries accompanying peripheral airways was related to the size of the perfusing vessel and showed greater variation within each case than did arterial muscularity. In the two injected specimens precise measurements of external diameter were made at all levels along the arterial pathway. In case 4, the intra-acinar arteries of the right lung supplied by normally connected pulmonary arteries into which a Goretex shunt had been inserted were of normal size (Fig. 4). By contrast, in three of the four segments perfused by different collateral arteries, the vessels were smaller than is found in the normal child at birth. The smallest arteries were seen in the right lower lobe perfused initially by collateral arteries which had been ligated at 18 days of age. In case 11, the intra-acinar arteries from the level of the terminal bronchioli to the alveolar walls were smaller at 3 years of age than in the normal lung at 6 months in all the five segments examined (Fig. 4).

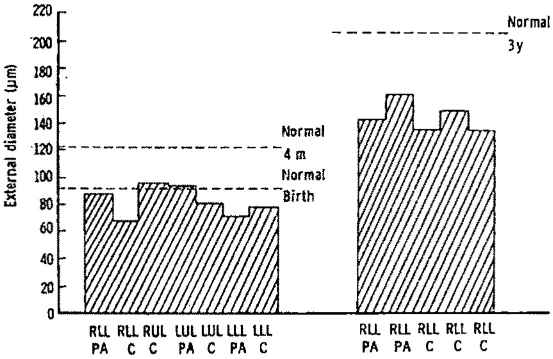

Fig. 4 *External diameter (µm) of arteries accompanying respiratory bronchioli in bronchopulmonary segments perfused either via central pulmonary arteries (PA) or collaterals (C), in case 4 on the left, and case 11 on the right. Both cases show a reduction in arterial size in nearly all segments of lung examined, as compared with findings in children of similar age.*

Arterial number

In both injected cases alveoli and arterial number per unit area was normal. In case 4, the alveolar/arterial ratio varied between 9·37 and 11·5 in six segments and in case 11, between 9·0 and 12·2 in the five segments examined.

Discussion

This is the first detailed study of the anatomy of the pulmonary circulation in pulmonary atresia with major aortopulmonary collateral arteries. Examination of 11 necropsy specimens showed, in all cases, central pulmonary arteries which had generally been perfused retrogradely by collateral arteries anastomosing with the lobar pulmonary arteries or, less commonly, with the pulmonary arteries at the hilum. Considering the group as a whole, normally connected pulmonary arteries perfused approximately half the bronchopulmonary segments. The remaining segmental arteries were connected to collateral arteries, which within the lung had the structure of normally connected pulmonary arteries and branched with the pre- and intra-acinar airways in the normal manner to perfuse the alveolar-capillary bed. Occasionally two intrapulmonary arteries, one connected to a central pulmonary artery and one to a collateral, accompanied a lobar or segmental bronchus, but after further airway division, the arteries diverged to accompany different airways. The segmental pulmonary arteries were generally abnormally small in relation to the size of the accompanying airway, irrespective of the type of proximal connection. Stenoses occurred in the majority of collateral arteries often as a thick narrowed segment between the aorta and lung.

Microscopically, the structural changes at the lung periphery were consistent with reduction in pulmonary blood flow in five of the nine cases examined, irrespective of the type of proximal connection. In three cases, medial hypertrophy suggested the presence of pulmonary hypertension. The peripheral pulmonary circulation had failed to grow normally in all save the patient who died at 12 days of age.

EMBRYOLOGY AND NOMENCLATURE

Major aortopulmonary collateral arteries have been variously called "bronchial arteries", "systemic arteries", and "persistent segmental arteries". The purely descriptive term major aortopulmonary collateral arteries has also been eschewed by some authors because in their series the vessels did not always originate from the aorta.[8] In the present study, however, nearly all the collateral arteries were seen to arise from the aorta. In addition, in eight cases bronchial arteries were seen to arise as a distinctly separate system from the tracheobronchial plexus around the carina and were distributed to the large airways in a normal manner. Four lobes containing bronchial arteries were perfused by collateral arteries arising from the descending thoracic aorta. Recent embryological studies by Boyden[9 10] suggest that major aortopulmonary collateral arteries are persistent segmental arteries, not bronchial arteries. The present study supports this hypothesis. During early fetal development the vascular plexus forming in the lung buds is connected to segmental arteries arising from the dorsal aortae. Within the lung, by the 40th day, the vascular plexus has differentiated into definitive segmental arteries and their branches,[11] and the lung is perfused both by the right ventricle and sixth branchial arches and by segmental arteries, until the latter disappear about 50 days after ovulation. Findings in the present study suggest that during this time some bronchopulmonary segments or lobules are connected to the right ventricle and others to the aorta. In the normal fetus, as the lung develops it becomes entirely and exclusively supplied by central pulmonary arteries derived from the sixth branchial arches. In pulmonary atresia with ventricular septal defect, however, it appears that the normal maturation process is arrested.

Nearly all the collateral arteries in the present series arose from the same region of the midthoracic aorta. Hessel *et al.*[12] considered that such arteries must have arisen *in utero* above the zone from which segmental arteries normally descend from the "neck" region of the embryo to below the diaphragm. These observations suggest that in the present series, normal fetal development was interrupted at about the same age in all cases. Furthermore, the primary abnormality appears to lie in the heart, and sixth branchial arches. The lung segment appears to have developed normally, as regards both arteries and airways, any structural change being the result of abnormalities in blood pressure and flow. None of the lung tissue in the present series was sequestrated, airway development being normal. Boyden[9] emphasised that collateral arteries developed early and bronchial arteries late, long after the blood supply to the lung is established. He described a 41 mm embryo in which the right posterobasal segment of lung was perfused by an aortic branch at a time when the origin of the bronchial arteries could be seen, but no vessels yet reached the root of the lung. In the present study bronchial arteries could be differentiated from major aortopulmonary collateral arteries because they were smaller and their origin could be traced to the vascular plexus around the carina and lower end of the trachea. Bronchial arteries probably enlarge because the centrally connected pulmonary arteries are, or become, extremely small. In three cases, arteries running down the lateral margin of the trachea entered the upper lobes, branched with the airways, and appeared to be the only blood supply to certain segments. The origin of these vessels is unknown.

COMPARISON OF PRESENT FINDINGS WITH PREVIOUS CLINICAL STUDIES

The first report of some segments of lung being perfused by central pulmonary arteries and others solely by a systemic artery is probably that of Joseph Hyrtle, published in 1839, in a child who did not have congenital heart disease.[12] More recently, radiological studies showed that this occurs in pulmonary atresia with ventricular septal defect.[13–15] The present study extends these observations by showing that the intrapulmonary arteries with which the collaterals connect are "true" pulmonary arteries, that not only the segments, but the subsegments of a lobe may have a different proximal connection, and that the proportion of a lung directly connected to a collateral artery can vary from 0 to nearly 100 per cent.

In this necropsy study central pulmonary arteries were present in all cases, perfused by major aortopulmonary collateral arteries joining a lobar or, less commonly, an extrapulmonary vessel. Theoretically, therefore, selective angiography of all collateral arteries would have shown central pulmonary arteries in all but one patient in whom the vessels were not patent. In practice, selective angiography usually does demonstrate central pulmonary arteries, but most authors note the exceptional case.[8 16 17]

In life, assessment of the adequacy of central pulmonary arteries for insertion either of a prosthetic shunt or a valve-bearing conduit is difficult. In the present study, the central pulmonary arteries were obviously small. Had they been distended before fixation they would still have been small relative to the size of the accompanying airway. Probably in only two cases, however, would the vessels have been too hypoplastic to take a prosthetic shunt. In a recent radiological study, the central pulmonary arteries were considered hypoplastic in relation to the size of the aortic root and vertebral bodies in 48 per cent of cases, but severe hypoplasia was not thought to contraindicate surgical treatment.[15] Findings in the present study suggest that even when the central pulmonary arteries are severely hypoplastic it may be possible to shunt to a larger hilar pulmonary artery.

The site of origin of the collateral arteries, and their extra- and intrapulmonary course was more constant in this than in other series,[8,15] and might be a result of the relatively small number of cases studied. There was, however, considerable variation between cases in the number of collateral arteries arising from the aorta, the number of branches arising from each collateral, and the number of bronchopulmonary segments connected to collateral arteries. Not surprisingly, in a necropsy study, the number of collaterals in each case tended to be greater than in previous radiological studies.[8,15] This observation is important because failure to show central pulmonary arteries is usually because of failure to appreciate the number of collaterals available for selective angiography, as many as six per case in this series. In addition, failure to identify all collaterals leads to an overestimation of the proportion of lung connected to central pulmonary arteries.

STENOSES

Stenoses of major aortopulmonary collateral arteries were first noted angiocardiographically by Jefferson *et al.*[13] and pressure gradients across them were documented the following year.[18] A stenosis can occur at the origin of a collateral from the aorta, along its course, and where it anastomoses with a pulmonary artery. Each collateral may have more than one stenosis. In a recent radiological study 42 per cent of all collateral arteries arising from the aorta were stenosed, affecting 70 per cent of patients.[15] In the present series a higher proportion (58·8%) of collaterals was stenosed and all patients had at least one stenosed vessel. In the radiological series, stenoses occurred most frequently at the junction of a collateral with a hilar pulmonary artery, and were present in 47 per cent of patients. In the present series a similar proportion of cases, 55 per cent, had this type of stenosis, but a narrowed segment occurred in all cases and accounted for 76 per cent of all stenoses.

Despite the incidence of stenosis being higher in this than in previous studies the incidence was probably underestimated. In nine of the 11 cases the arteries were not distended by injection and though all collaterals were examined carefully macroscopically, only 13 were examined microscopically by step or serial sections. In addition, in the two injected cases radiological assessment yielded a disproportionately greater number of stenosed collateral arteries than in the uninjected material.

Occasionally the lumen of a collateral was occluded, because of the fusion of intimal mounds or cushions in a long narrow segment: Obviously, when this happens the distal patent segment of a collateral artery anastomosing with a very small, but structurally normal intrapulmonary artery, cannot be shown radiologically, except, perhaps, by pulmonary vein angiography.[19]

When planning either to shunt to a region of lung perfused by a collateral artery or to connect such a portion of lung to the sixth arch it is necessary to check for the presence of stenoses both by intravascular pressure measurement, by angiography, and by palpation of the vessel at operation. The latter is helpful in detecting a thick-walled, narrowed segment. In life, the radiographic appearance of the vessels is unreliable in assessing the haemodynamic state. Macartney *et al.*[14] found a pressure gradient of 60 mm or more in vessels in which angiography had failed to reveal a stenosis.

Stenoses of the intrapulmonary arteries were not seen in the present series. Though they could have been overlooked in fixed undistended material, they were not shown either macroscopically or radiologically in the two injected cases.

STRUCTURE OF INTRAPULMONARY ARTERIAL CIRCULATION

Preacinar arteries

The preacinar arteries, both those connected to collateral arteries and those connected to central pulmonary arteries, were generally abnormally small, both absolutely and in relation to the size of the accompanying airway. Three children had had a surgical aortopulmonary or aortocollateral anastomosis created. After an aortopulmonary anastomosis in two, the distal lobar pulmonary artery appeared larger than in the untreated cases and was normal relative to the size of the accompanying airway. Unfortunately, however, in both cases the distal vessel perfused only five bronchopulmonary segments or less, and in one child the dilated lobar and segmental arteries severely compressed the right middle lobe and lower lobe bronchi. In the other patient a large aortopulmonary anastomosis failed to perfuse the contralateral lung because the central pulmonary arteries were barely probe patent. These findings emphasise the necessity of careful preoperative evaluation by selective angiography.

In two cases one lobar pulmonary artery and its segmental branches showed saccular dilatation. This appearance is seen not infrequently during life after a successful aortopulmonary anastomosis (personal observation). Its presence in two untreated cases indicates that such dilatation can occur as a primary abnormality of the vessel wall in pulmonary atresia with ventricular septal defect and major

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aortopulmonary collateral arteries, and is not necessarily a result of an increase in pulmonary blood flow.

Intra-acinar arteries

In the normal child most of the intra-acinar arteries develop after birth, during the first three years of life.[4] The haemodynamic abnormalities produced by a variety of different types of congenital heart disease are known to impair the normal development of these vessels.[20–22] The present study shows that pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries is no exception.

Peripheral pulmonary vascular structure determines resistance and hence operability, but this is the first time that vessel growth has been assessed in this condition where different segments of lung frequently have a different blood supply. Greater accuracy is achieved by studying injected rather than uninjected material, but examination of both types of tissue gave similar results. Within each case arterial muscularity, size, and number were surprisingly similar in segments of lung perfused by normally connected pulmonary arteries and by collaterals. This probably occurred because the majority of segments were underperfused and because most of the patients were infants, the lung having been exposed to abnormalities of pressure or flow for a relatively short period of time. Case 11 illustrates the variation in pulmonary vascular structure which can develop by 3 years of age, even within a segment of lung perfused by a single vessel. Abnormally thin-walled arteries lay adjacent to others showing concentric intimal proliferation, probably resulting from organisation of thrombus.

Most cases showed normal or reduced pulmonary arterial medial thickness and external diameter and, in three cases, the vessels contained areas of eccentric intimal proliferation. All these structural changes are compatible with a reduction of pulmonary blood flow.[23–25] In at least two cases, however, any reduction in flow or pressure was not sufficient to impair arterial multiplication.

Structural evidence of pulmonary hypertension was found in only three cases and was not severe. The only case to show early intimal proliferation had had a Blalock-Taussig shunt to one region and a larger collateral supplying another region of lung examined. Previous studies have emphasised the danger of large collateral arteries without a protective stenosis perfusing the pulmonary vascular bed at high pressure and causing obliterative pulmonary vascular disease.[13 14] The prevalence of pulmonary hypertensive change probably depends on the age of the patients in each series. Patients who live longer presumably have larger collateral arteries and a higher pulmonary blood flow than in the present series, making them susceptible to obliterative change.

The present study indicates that though stenoses in the collateral arteries "protect" the pulmonary vascular bed from developing hypertensive pulmonary vascular change they may also prevent the lung from being adequately perfused, causing failure of the intra-acinar pulmonary circulation to develop normally. Such a lung may not be capable of accepting an increase in blood volume, as after an aortopulmonary anastomosis or insertion of a right ventricular conduit, without an increase in resistance. In infants with a large ventricular septal defect an increase in resistance is associated first with failure of the peripheral pulmonary circulation to grow normally, before obliterative pulmonary vascular disease develops.[22]

CLINICAL IMPLICATIONS

Findings in the present study are helpful in understanding the natural history of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. The rapid increase in cyanosis frequently seen during the first weeks of life is often attributed to closure of the ductus arteriosus, but the role of the ductus in this condition depends on the proportion of lung connected to the central pulmonary arteries. Increasing cyanosis may also be a result of progressive stenosis of the collateral arteries. In older children the picture is more complex. Increasing cyanosis may be a result either of failure of the collateral to increase in size with growth of the child, particularly in stenosed regions, of failure of the intrapulmonary arterial circulation to grow normally, or of thrombus formation in some peripheral arteries and obliterative pulmonary vascular disease in others. In any child the clinical findings and total pulmonary vascular resistance are the sum of the changes taking place in each segment of lung tissue.

The anatomical findings are so variable in pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries that all cases must be considered individually. In order to plan effective treatment a cardiac catheterisation study is advisable at the first hospital admission. If possible, all the collateral arteries should be catheterised in order to demonstrate the central pulmonary arteries and the proportion of lung connected to them. Ideally, the blood supply of each bronchopulmonary segment should be visualised and the intrapulmonary arterial pressure measured.

Correction of the abnormality is usually undertaken as a two-stage procedure. The aim of the first-stage operation is to increase pulmonary blood flow in order to allow the child to thrive and to encourage the pulmonary circulation to grow and develop normally. An aortopulmonary shunt is inserted, if possible, into a centrally connected pulmonary artery which is known to perfuse the majority of bronchopulmonary segments of one lung and to be connected through a good lumen with the contralateral lung. Any shunt into a collateral vessel should be performed distal to any stenosis, that is, into the thin-walled elastic pulmonary artery beyond the collateral. This should ensure that the blood supply will not be prejudiced by any further occlusive change in the collateral vessel. Before correcting the abnormality by connecting the pulmonary arterial circulation to a right ventricular conduit as many bronchopulmonary segments as possible should be connected to the main perfusing vessel, hopefully a central pulmonary artery or one of its major branches. Postoperatively, in tetralogy of Fallot with pulmonary atresia the mortality is greater, and the right ventricular pressure is higher, in patients with large collateral arteries than in those without them and the postoperative right ventricular/left ventricular pressure ratio, itself a strong predictor of operative survival, is much increased in the presence of "arborisation abnormalities" particularly when these are bilateral.[26] Since "arborisation abnormalities" presumably indicate the presence of collaterals not connected to central pulmonary arteries, bilateral arborisation abnormalities were present in nearly all the patients we studied.

Ideally, collateral arteries supplying a substantial volume of the pulmonary vascular bed should be reconnected and not ligated. Ligation of an isolated collateral is effectively ligation of an intrapulmonary artery which is known to produce hypertrophy of the bronchial arterial circulation.[27] Gas exchange can occur in such a lung, but the normal architecture of the intrapulmonary arterial circulation is permanently destroyed. However, ligation of such a collateral may be preferable to leaving it unligated if it cannot be connected directly or indirectly to central pulmonary arteries. The rationale for this is that interruption of one pulmonary artery causes hypoplasia of the ipsilateral lung and enlargement of the contralateral lung.[28] Thus bronchopulmonary segments connected to pulmonary arteries may come to compose a greater proportion of the entire lung issue than they would have done had not the isolated major aortopulmonary collateral artery or arteries been ligated.

After corrective surgery a rise in right ventricular pressure might be the result of any one or more of the following features: (a) failure of the right ventricle to perfuse the majority of bronchopulmonary segments; (b) proximal or distal pulmonary artery stenosis; (c) failure of the central and peripheral pulmonary arterial circulation to grow and develop normally; and (d) obliteration of pulmonary vessels, either secondary to hypoperfusion or to pulmonary hypertension.

This paper provides a rational basis for treatment, but the practical difficulties encountered in investigating and treating these patients will doubtless prevent total correction in many cases. In the fortunate child, however, at a second stage operation the right ventricle would be connected to low-pressure central pulmonary arteries perfusing the majority of bronchopulmonary segments.

References

1 Davies G, Reid L. Growth of the alveoli and pulmonary arteries in childhood. *Thorax* 1970; **25:** 669–81.

2 Hislop A, Reid L. New pathological findings in emphysema of childhood: 1. Polyalveolar lobe with emphysema. *Thorax* 1970; **25:** 682–90.

3 Foster-Clark AF. *Chest diseases.* vol 1. London: Butterworths, 1963: 19, 21–2.

4 Hislop A, Reid L. Pulmonary arterial development during childhood: branching pattern and structure. *Thorax* 1973; **28:** 129–35.

5 Rabinovitch M, Haworth SG, Castaneda AR, Nadas AS, Reid LM. Lung biopsy in congenital heart disease: a morphometric approach to pulmonary vascular disease. *Circulation* 1978; **58:** 1107–22.

6 Haworth SG. Collateral arteries in pulmonary atresia with ventricular septal defect: a precarious blood supply. *Br Heart J* 1980; **44:** 5–13.

7 Anderson EG, Simon G, Reid L. Primary and thrombo-embolic pulmonary hypertension: a quantitive pathological study. *J Pathol* 1973; **110:** 273–93.

8 McGoon DC, Baird DK, Davis GD. Surgical management of large bronchial collateral arteries with pulmonary stenosis or atresia. *Circulation* 1975; **52:** 109–18.

9 Boyden EA. The time lag in the development of bronchial arteries. *Anat Rec* 1970; **166:** 611–4.

10 Boyden EA. The developing bronchial arteries in a fetus of the twelfth week. *Am J Anat* 1970; **129:** 357–68.

11 Wells LJ, Boyden EA. The development of the bronchopulmonary segments in human embryos of Horizons XVII to XIX. *Am J Anat* 1954; **95:** 163–201.

12 Hessel EA, Boyden EA, Stamm SJ, Sauvage LR. High systemic origin of the sole artery to the basal segments of the left lung: findings, surgical treatment and embryologic interpretation. *Surgery* 1970; **67:** 624–32.

13 Jefferson K, Rees S, Somerville J. Systemic arterial supply to the lungs in pulmonary atresia and its relation to pulmonary artery development. *Br Heart J* 1972; **34:** 418–27.

14 Macartney FJ, Scott O, Deverall PB. Haemodynamic and anatomical characteristics of pulmonary blood supply in pulmonary atresia with ventricular septal defect—including a case of persistent fifth aortic arch. *Br Heart J* 1974; **36:** 1049–61.

15 McGoon MD, Fulton RE, Davis GD, Ritter DG, Neill CA, White RI Jr. Systemic collateral and pulmonary artery stenosis in patients with congenital pulmonary valve atresia and ventricular septal defect. *Circulation* 1977; **56:** 473–9.

16 Chesler E, Beck W, Schrire V. Selective catheterization of pulmonary or bronchial arteries in the preoperative assessment of pseudotruncus arteriosus and truncus arteriosus type IV. *Am J Cardiol* 1970; **26:** 20–4.

17 Berry BE, McGoon DC, Ritter DG, Davis GD. Absence of anatomic origin from heart of pulmonary arterial supply: clinical application of classification. *J Thorac Cardiovasc Surg* 1974; **68:** 119–25.

18 Macartney F, Deverall P, Scott O. Haemodynamic characteristics of systemic arterial blood supply to the lungs. *Br Heart J* 1973; **35:** 28–37.

19 Singh SP, Rigby ML, Astley R. Demonstration of pulmonary arteries by contrast injection into pulmonary vein. *Br Heart J* 1978; **40:** 55–57.

20 Haworth SG, Reid L. Quantitative structural study of pulmonary circulation in the newborn with pulmonary atresia. *Thorax* 1977; **32:** 129–33.

21 Haworth SG, Reid L. A structural study of the pulmonary circulation and of the heart in total anomalous pulmonary venous return in early infancy. *Br Heart J* 1977; **39:** 80–92.

22 Haworth SG, Sauer U, Bühlmeyer K, Reid L. The development of the pulmonary circulation in ventricular septal defect: a quantitative structural study. *Am J Cardiol* 1977; **40:** 781–8.

23 Civin WH, Edwards JE. Pathology of the pulmonary vascular tree. I. A comparison of the intra-pulmonary arteries in the Eisenmenger syndrome and in stenoses of ostium infundibuli associated with biventricular origin of the aorta. *Circulation* 1950; **2:** 545–52.

24 Best PV, Heath D. Pulmonary thrombosis in cyanotic congenital heart disease without pulmonary hypertension. *J Pathol Bacteriol* 1958; **75:** 281–91.

25 Naeye RL. Perinatal changes in the pulmonary vascular bed with stenosis and atresia of the pulmonic valve. *Am Heart J* 1961; **61:** 586–92.

26 Alfieri O, Blackstone EH, Kirklin JW, Pacifico AD, Bargeron LM Jr. Surgical treatment of tetralogy of Fallot with pulmonary atresia. *J Thorac Cardiovasc Surgery* 1978; **76:** 321–35.

27 Liebow AA, Hales MR, Bloomer WE, Harrison W, Lindskog GE. Studies on the lung after ligation of the pulmonary artery. II. Anatomical changes. *Am J Pathol* 1950; **26:** 177–95.

28 Pool PE, Vogel JHK, Blount SG. Congenital unilateral absence of a pulmonary artery. The importance of flow in pulmonary hypertension. *Am J Cardiol* 1962; **10:** 706–32.

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References: 1. *Cardiovascular Medicine*, Jan. 1978, p. 45 (41-56), **Vol. 3,** No. 1. 2. *Drugs* (review article), 1977, 14, 163-197. 3. *Postgraduate Medicine*, Nov. 1975, p. 117-127. 4. *Circulation*, 1968, **38**, 164. 5. Proceedings of a Symposium held at the Centre Interprofessionel, Geneva, 8th March, 1974. 6. *Drugs* (review article),

Br Heart J 1980; **44:** 25–9

Excessive plasma dopamine increase at rest and during exercise after long-term beta-adrenoreceptor blockade in hypertensive patients

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SUMMARY The effect of four weeks and 15 months of treatment with the cardioselective beta-receptor antagonist metoprolol on blood pressures, plasma noradrenaline, adrenaline, and dopamine at rest, during submaximal steady state and near maximal exercise, as well as five minutes after exercise, was studied in seven moderately hypertensive men aged 25 to 51 years.

Four weeks of treatment resulted in significantly lower heart rates and blood pressures at rest, during, and after exercise; no further significant changes were observed after 15 months of continuous treatment.

The exercise-induced increase in plasma noradrenaline and adrenaline tended to be more pronounced after treatment with metoprolol with virtually identical values after both four weeks and 15 months. Plasma dopamine was much less affected by exercise and showed only a weak tendency towards higher values during work. While no significant changes were observed after four weeks of treatment, there was a significant 10 to 12 fold increase of dopamine over the control values after 15 months of treatment. At rest plasma dopamine was five and 10 times higher than corresponding noradrenaline and adrenaline levels. The excessive rise of dopamine might have clinical implications: because of the cardiovascular and renal actions of dopamine, high levels should tend towards dampening the negative inotropic effect of beta-receptor blockade and might thus contribute to the increase of cardiac output and decrease of peripheral vascular resistance usually seen with beta-receptor antagonists after long-term treatment compared with acute or short-term administration.

Antihypertensive treatment with adrenergic beta-receptor antagonists has been shown to give rise to higher levels of plasma noradrenaline during exercise of different intensities.[1–3] Conversely, a significant rise of adrenaline has been observed only during near maximal work and was interpreted as reflecting secondary metabolic adjustments to the beta-receptor blockade.[2 4 5] With a few exceptions[3] these observations were made after acute administration of a beta-receptor antagonist or after short-term treatment. Very little interest has been shown in plasma dopamine. Though dopamine has been the subject of considerable theoretical and clinical interest and research in recent years because of its specific cardiovascular and renal effects,[6–8] in particular in association with shock, no data are available on the response of plasma dopamine to long-term beta-receptor blockade.

The purpose of the present study is therefore to define the effect of the cardioselective beta-receptor blocker metoprolol on the response to standardised exercise of plasma noradrenaline, adrenaline, and in particular dopamine after long-term treatment compared with short-term treatment.

Patients

Seven men aged 25 to 51 (mean 35) years participated in the study after giving their informed consent. Clinical evaluation indicated that all had stage 1 to 2 essential hypertension using criteria described by the WHO (1959).[9] None suffered from ischaemic heart disease. Blood pressures when measured by the Riva-Rocci cuff method

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ranged between 155 ±10/101 ±4 (means and standard deviations) mmHg at rest supine and 236 ±30/112 ±13 mmHg during near-maximal exercise (Table).

Methods

After initial investigation, treatment was started with a daily dose of 200 mg oral metoprolol and was maintained without any change during the entire observation period. The patients were studied again after a four-week and subsequently a 15-month period of treatment under identical conditions and with identical technique as in the initial study. On each occasion, the patients exercised at their individual work loads established during the initial investigation.

On arrival at the laboratory, a polyvinyl catheter was inserted percutaneously via an antecubital vein and the tip positioned in the superior vena cava in order to facilitate blood sampling. After 30 minutes of rest in the supine position, exercise was performed sitting on an electrodynamically braked bicycle ergometer at a rate of 60 rpm, starting at 50 watts with a 10 watt increment every minute until a heart rate of approximately 130 was attained. The patients then continued exercising at the same load under steady state conditions for a further 24 minutes. Subsequently, work loads were increased by 25 watt increments every minute and the test concluded by a one-minute work at maximal level. In three patients, however, true maximal work load could not be attained because of an excessive blood pressure response (systolic pressure exceeding 270 mmHg). This final phase usually lasted four to five minutes. Pulse rates (auscultatory method) and systolic and diastolic blood pressures (Riva-Rocci cuff method) were recorded and blood samples were obtained after 30 minutes of supine lying, during the sixth minute at work load 100 watts, during the 30th minute of submaximal steady state exercise, during near-maximal exercise, and five minutes after work in the sitting posture.

Plasma catecholamines were determined by means of an enzymatic single isotope method[10] with a coefficient of variation ranging for noradrenaline and adrenaline between 5 and 10 per cent at high and low levels, respectively, and for dopamine between 8 and 14 per cent.[11] Student's t test for paired samples was used for statistical analysis.

Results

Heart rate, and systolic and diastolic blood pressures were significantly ($p < 0{\cdot}01$) reduced at rest and during exercise after four weeks of treatment with metoprolol compared with pretreatment values. No further significant changes were observed after 15 months of continuous treatment; however, there was a clear tendency toward lower diastolic blood pressures during and after exercise (Table).

The exercise-induced increase of plasma noradrenaline tended to be more pronounced after treatment with metoprolol; individual and mean values were virtually identical at four weeks and 15 months (Fig. 1).

The effect on plasma adrenaline was similar; the rise as observed particularly during near-maximal work was of the same order after four weeks and 15 months (Fig. 2).

The levels of plasma dopamine were much less affected by exercise (Fig. 3) and showed only a weak tendency towards higher values during exercise. While no significant changes were observed after four weeks of treatment, there was a significant ($p < 0{\cdot}001$) 10 to 12 fold increase of plasma dopamine over control values after 15 months of treatment with roughly identical levels during all conditions.

Table *Heart rates (HR, beats/min), systolic (SBP, mmHg), and diastolic (DBP, mmHg) blood pressures before and after four weeks and 15 months of treatment with metoprolol (means ± standard deviations, n = 7)*

		Rest supine	*Exercise 6 min*	*Exercise 30 min*	*Exercise near-max*	*Post-exercise 5 min sitting*
Pretreatment	HR	74 ±7	117 ±14	136 ±4	173 ±12	106 ±19
	SBP	155 ±10	210 ±27	202 ±29	236 ±30	156 ±15
	DBP	101 ±4	115 ±15	106 ±7	112 ±13	92 ±14
Metoprolol four weeks	HR	57 ±10**	93 ±11**	100 ±8**	123 ±9**	77 ±10**
	SBP	130 ±7**	154 ±20**	164 ±19**	200 ±20**	127 ±13**
	DBP	86 ±7**	98 ±8**	96 ±9**	108 ±12	84 ±10
Metoprolol 15 months	HR	52 ±11	87 ±17	98 ±13	125 ±17	70 ±17
	SBP	132 ±12	150 ±13	158 ±19	190 ±29	127 ±11
	DBP	90 ±9	91 ±7	90 ±8	101 ±10*	80 ±5*

Asterisks denote level of statistical significance of changes from previous examination *$p < 0{\cdot}05$, **$p < 0{\cdot}01$.

At rest, before exercise, plasma dopamine was five and 10 times higher than corresponding plasma noradrenaline and adrenaline levels (Fig. 4) ($p < 0{\cdot}001$) and of the same magnitude as plasma noradrenaline during exercise at 100 watts as well as five minutes after exercise.

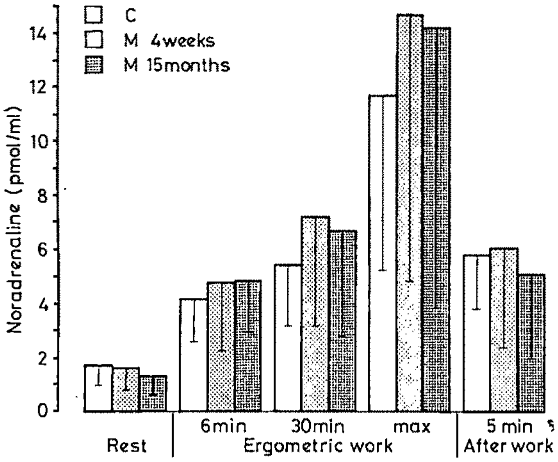

Fig. 1 *Plasma noradrenaline at rest supine; during submaximal and near-maximal work; and five minutes after exercise; before and after a four-week and 15-month period of treatment with metoprolol (means and standard deviations, n = 7).*
The six-minute exercise corresponds to a work load of 100 watts, the 30-minute exercise to steady state work at a heart rate of approximately 130 beats/minute under pretreatment conditions.

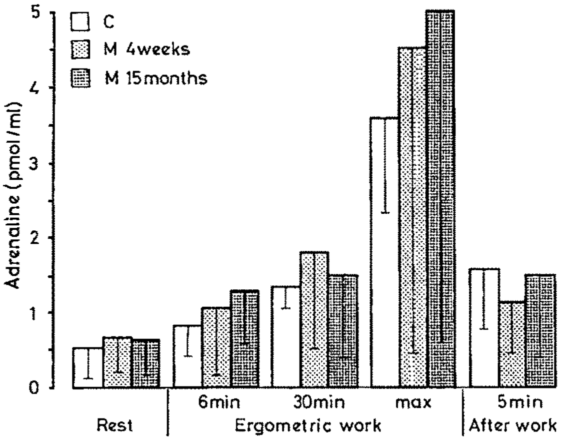

Fig. 2 *Plasma adrenaline at rest supine; during submaximal and near-maximal work; and five minutes after exercise; before and after a four-week and 15-month period of treatment with metoprolol. For further details see Fig. 1.*

Discussion

Treatment with the cardioselective adrenoreceptor blocking agent metoprolol resulted in considerably lower blood pressures and pulse rates at rest as well as during and after exercise. Normotension was attained in virtually all patients. The extent of

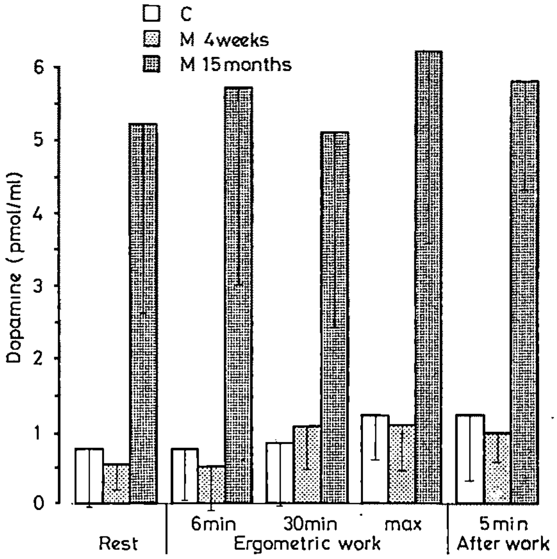

Fig. 3 *Plasma dopamine at rest supine; during submaximal and near-maximal work; and five minutes after exercise; before and after a four-week and 15-month period of treatment with metoprolol. For further details see Fig. 1.*

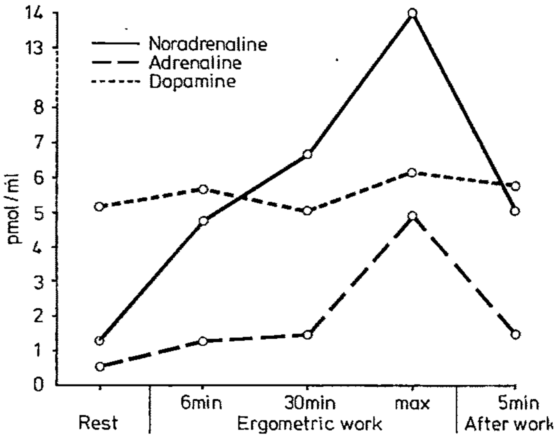

Fig. 4 *Means of plasma noradrenaline, adrenaline, and dopamine at rest supine; during submaximal and near-maximal work; and five minutes after exercise; after a 15-month period of treatment with metoprolol.*

pulse rate and systolic blood pressure reduction was almost identical after the four-week and 15-month periods. Only diastolic pressures showed a tendency towards a further slight decrease after 15 months compared with four weeks of treatment.

The fairly constant effect of treatment on the circulation during standardised exercise as evident from the similar pulse rates and blood pressures observed at four weeks and 15 months of treatment is particularly worth noting as it is of great importance when the response of plasma catecholamines to exercise and to treatment of different durations is to be evaluated.[5]

The changes in plasma noradrenaline and adrenaline observed after four weeks of beta-receptor blockade in the present series agree with the results reported by other authors.[1 3 12] The results obtained at four weeks and 15 months, respectively, in our patients indicate that the changes in both plasma noradrenaline and adrenaline induced by beta-receptor blockade remain virtually constant independently of the duration of treatment. Despite unchanged levels of plasma noradrenaline, the diastolic blood pressure tended to be slightly lower after 15 months compared with that at four weeks. This might suggest that levels of circulating noradrenaline do not play a primary or decisive role in the mechanism of the antihypertensive effect exerted by beta-receptor blocking agents.[5] Even adrenaline does not seem to be of major importance in this respect. The increase of plasma adrenaline after beta-receptor blockade, in particular under conditions of near maximal exercise, reflects a compensatory mechanism aimed at coping with the restricted glycogen breakdown in the working muscle during heavy work.[2 5]

Plasma dopamine was virtually unchanged after four weeks of metoprolol administration but it showed a considerable rise after 15 months of treatment. The dopamine levels attained are of such an order that haemodynamic effects resulting from the specific properties of dopamine,[7] are likely to occur[13] and might have clinical implications. Dopamine has a positive effect on the cardiac contractility resulting in a significant increase in stroke volume and cardiac output.[7 8 13] Furthermore, dopamine is a potent vasodilator of the renal vascular bed inducing increased perfusion mainly in the renal medulla[14] and a significant enhancement of sodium excretion.[6 7] Because of these specific effects high levels of dopamine should tend towards dampening the negative inotropic effect of chronic beta-receptor blockade. Hence it might contribute to the increase of cardiac output and the decrease of peripheral vascular resistance seen after long-term treatment compared with acute or short-term administration of most beta-receptor blockers,[15 16] and even alpha-beta-receptor blockers.[17]

Furthermore, the high levels of dopamine may tend to counterbalance the reduced hypothalamic dopaminergic activity shown to occur in hypertensives and to be influenced by the dopaminergic agonist bromocriptine.[18]

It is important to underline that these findings are preliminary; since different beta-receptor blockers may have different effects on plasma catecholamines[5] they may not apply to all beta-receptor antagonists. Thus, the finding of an excessive dopamine increase during chronic adrenergic beta-receptor blockade requires further confirmation and research.

References

[1] Irving MH, Britton BJ, Wood WG, Padgham C, Carruthers M. Effects of β-adrenergic blockade on plasma catecholamines in exercise. *Nature* 1974; **248:** 531–3.

[2] Galbo H, Holst J, Christensen NJ, Hilsted J. Glucagon and plasma catecholamines during beta-receptor blockade in exercising man. *J Appl Physiol* 1976; **40:** 855–62.

[3] Hansson B-G. Long-term non-selective and cardioselective beta-receptor blockade in hypertensive patients. *Acta Med Scand* 1976; suppl 598.

[4] Franz I-W, Lohmann FW, Koch G, Röcker L. Effect of non-selective and cardioselective beta-receptor blockade on metabolism during exercise in hypertensive men (in German). *Verh Dtsch Ges Inn Med* 1978; **84:** 813–6.

[5] Franz I-W, Lohmann FW, Koch G. Differential effects of long-term cardioselective and non-selective beta-receptor blockade on plasma catecholamines during and after physical exercise. *J Cardiovasc Pharmacol* 1980; **2:** 35–44.

[6] McDonald RH Jr, Goldberg LI, McNay JL, Tuttle EP Jr. Effect of dopamine in man: augmentation of sodium excretion, glomerular filtration rate and renal plasma flow. *J Clin Invest* 1964; **43:** 1116–24.

[7] Goldberg LI. Cardiovascular and renal actions of dopamine: potential clinical applications. *Pharmacol Rev* 1972; **24:** 1–29.

[8] Ramdohr B, Biamino G, Schüren KP, Schröder R. Dopamin bei der Behandlung der akuten schweren Herzinsuffizienz. *Med Welt* 1975; **26:** 540–7.

[9] World Health Organization. Prevention and control of arterial hypertension. *WHO Tech Rep Ser* 1959; **168:** 4–9.

[10] Koch G. Plasma renin activity, epinephrine and norepinephrine at rest and during exercise in young adults and boys (abstract). *Scand J Clin Lab Invest* 1977; **37** Suppl 147: 107.

[11] Koch G, Johansson U, Arvidson E. Radioenzymatic determination of epinephrine, norepinephrine and dopamine in 0·1 ml plasma samples. Plasma catecholamine response to submaximal and near maximal exercise. *J Clin Chem Clin Biochem* 1980; **18:** 367–72.

[12] Grobecker H, Planz G, Wiethod G, *et al.* Specific and non specific effects of β-adrenoreceptor blocking drugs in man (in German). *Klin Wochenschr* 1976; **54:** 783–8.

[13] Schmidt HD, Hoppe H, Heidenreich L. Direct effects of dopamine, orciprenaline and norepinephrine on the right and left ventricle of isolated canine hearts. *Cardiology* 1979; **64:** 133–48.

[14] Beckenridge A, Orme M, Dollery CT. The effect of dopamine on renal blood flow in man. *Eur J Clin Pharmacol* 1971; **3:** 131–6.

[15] Tarazi RC, Dustan HP. Beta adrenergic blockade in hypertension. Practical and theoretical implications of long-term hemodynamic variations. *Am J Cardiol* 1972; **29:** 633–40.

[16] Frisk-Holmberg M, Juhlin-Dannfeldt A, Jorfeldt L, Aström H. Effect of long-term antihypertensive beta-receptor blocking treatment on haemodynamic and metabolic responses to prolonged exercise in man. *Clin Sci Mol Med* 1976; **51:** 489–91.

[17] Koch G. Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol. *Br Heart J* 1979; **41:** 192–8.

[18] Kolloch R, Stumpe KO, Higuchi M, Vetter H, Krück F. Raised plasma-prolactin levels in essential hypertension: index of reduced hypothalamic dopaminergic activity? (in German). *Klin Wochenschr* 1977; **55:** 1013–8.

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Classification of the radiological morphology of the mitral valve

Differentiation between true and pseudoprolapse[*]

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SUMMARY The morphology of the mitral valve apparatus was assessed on 100 normal left ventriculograms. Four distinct types of mitral valve were identified according to the position of the mitral fulcrum (the point of attachment of the leaflets to the annulus) and the configuration of the adjacent left ventricular wall (left ventricular fornix) during diastole. Types I and II closely simulated prolapse of the mitral valve (pseudoprolapse) in the right anterior oblique projection during the ejection period. Measurements showed that contraction of the ventricle failed to reduce the diameter of the mitral valve annulus in 26 per cent of normal left ventricles.

The normal and pathological anatomy of the human mitral valve has been studied extensively, particularly at necropsy, but the normal dynamic anatomy remains elusive. A thorough knowledge of the changes occurring in the normal mitral valve apparatus during both diastole and systole is essential particularly for making the correct angiocardiographic diagnosis of mitral valve prolapse. In this report we describe the appearances of normal mitral valves during ventriculography and establish criteria for the identification of the normal mitral valve.

Subjects and methods

The biplane left ventriculograms of 100 patients with chest pain were analysed to determine the dynamic anatomy of the mitral valve. None of the patients had clinical or radiological evidence of mitral valve disease or papillary muscle dysfunction. The left ventricle was catheterised by the percutaneous transfemoral technique[1–3] with a polyurethane pigtail catheter, and 10 to 16 ml/s 76 per cent sodium-methylglucamine diatrizoate (Renografin 76) was injected in three seconds using a Viamonte/Hobbs automatic injector. The 6-inch modes of biplane 10 6-inch caesium-iodide Siemens high resolution image intensifiers (4·5 line pairs/mm resolution) were used with high definition photography of the output phosphor. The electrocardiogram and pressure pulses were simultaneously recorded on paper and on the cine film. Echocardiograms and phonocardiograms were obtained in all patients using a Hoffrel Ultrasonoscope (Model 101), with either a 2·25 MHz transducer focused at 7·5 cm or an unfocused 2·9 MHz transducer, and a piezoelectric crystal microphone (type 53161, Kent Cambridge, Ossining, NY), displayed on the oscilloscope of a Cambridge multichannel recorder, and permanently recorded on photographic paper. Prolapse of the mitral valve, mid-systolic clicks, and late systolic murmurs were specifically sought. Echocardiograms, phonocardiograms, and cine left ventriculograms were interpreted independently, and the results then pooled.

The configuration of the normal mitral valve and its dynamic changes were examined by tracing the image directly from projections of 16 mm cine film. Actual heart size was determined by the 1 cm grid technique (North American Medical Instrument Corp, Hudson Falls, NY). The outline of the left ventricle was traced at end-diastole and end-systole during the beat with optimal ventriculographic opacification. Premature ventricular contractions and post-extrasystolic contractions were excluded.

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Observations were made on: (1) changes in mitral valve diameter; (2) position of the point of attachment of the posterior leaflet of the mitral valve to the mitral ring in diastole and systole; (3) delineation of the papillary muscles and chordae tendineae; (4) mitral leaflets and their scallops; and (5) posteromedial and anterolateral commissures. The percentage shortening of the mitral valve ring diameter between diastole and systole was calculated in all cases. The depth of bulging of the mitral valve leaflets into the left atrium was measured in all patients.

The mitral fulcrum was defined as the point of attachment of the mitral leaflets to the annulus fibrosus. For the purposes of clarity the word "fulcrum" as used in this paper refers to the most inferior portion of the fulcrum as seen in the right anterior oblique projection (Fig. 1). The fornix of the left ventricle is defined as that part of the left ventricle between insertion of the mitral leaflets into the annulus fibrosus and the base of the papillary muscles. Ventriculography clearly delineates the fulcrum during the rapid filling phase of the cardiac cycle. The mitral fulcrum is seen at the interface formed by the unopacified blood rushing into the left ventricle and by the contrast trapped in the recess between the mitral leaflets and the adjacent ventricular endocardium (Fig. 1). The intimate relation of the most inferior portion of the mitral fulcrum to the posteromedial scallop of the posterior leaflet makes this portion of the fulcrum the best landmark for judging prolapse of the posteromedial scallop of the posterior leaflet. The posteromedial scallop is that most frequently involved in mitral valve prolapse.[4 5] The ability to visualise the mitral fulcrum during cineangiocardiography is the crux of this study and removes the subjective character of identification of mitral prolapse. The mitral fulcrum must be visualised in order to assess mitral valve prolapse objectively.

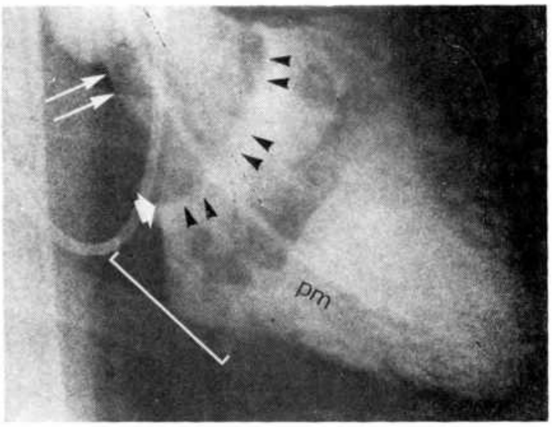


Fig. 1 *Early diastolic frame of a 16 mm cine left ventriculogram from a patient without heart disease. The fulcrum* (short wide white arrow) *or point of attachment of the mitral leaflets to the mitral annulus is clearly seen. The fornix* (white bracket) *is the left ventricular wall between the fulcrum and papillary muscles (pm). The papillary muscles are better seen on a systolic frame. Because of the high lying fulcrum and absence of notching of the fornix, this mitral valve has the type III configuration. The line of attachment of the posterior mitral leaflet* (black arrow-heads) *sharply outlines the width of the mitral valve. The membranous septum (atrioventricular portion)* (long thin white arrows) *can be seen in the subaortic region as a smooth straight or minimally curved line beneath the noncoronary leaflet. Unopacified left atrial blood entering into the left ventricle can be seen as the broad band of lucency encompassing the entire width of the ventricle and immediately in front of the attachment of the posterior mitral leaflet.*

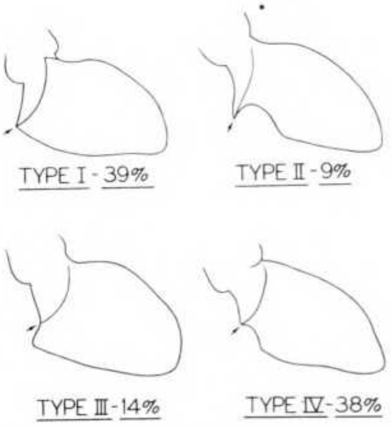


Fig. 2 *Diagrams of diastolic frames of left ventriculograms demonstrating the four mitral valve configurations. The arrows identify the mitral valve fulcra. Types I and II have low fulcra, but II has a notched fornix. Types III and IV both have high fulcra, and the fornix is also notched in type IV. Types I and IV are more common than types II and III.*

Results

Four distinct types of mitral valve were identified in the right anterior oblique projection, depending on the position of the mitral fulcrum in protodiastole and the diastolic configuration of the fornix of the left ventricle (Fig. 2). Type I was characterised by a low-lying mitral fulcrum without notching of the ventricular fornix. Type II had a low-lying mitral fulcrum and a semilunar notch in the left ventricular fornix. In type III there was a high

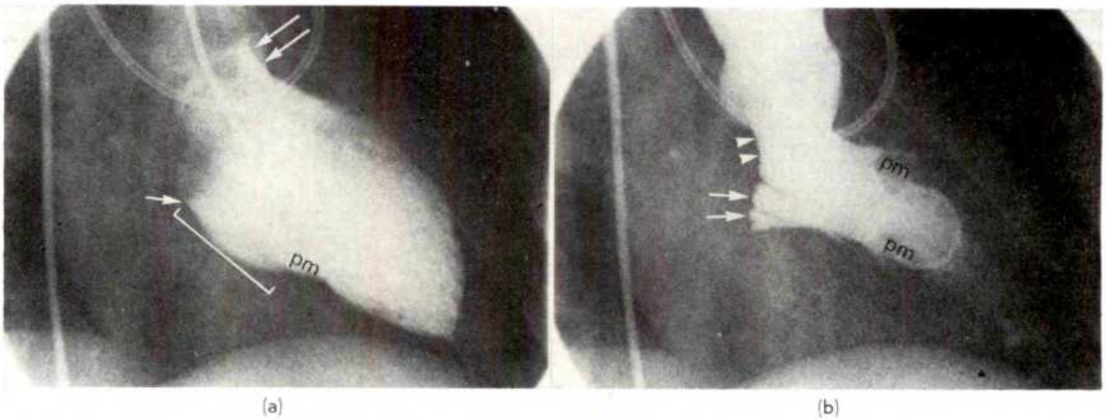


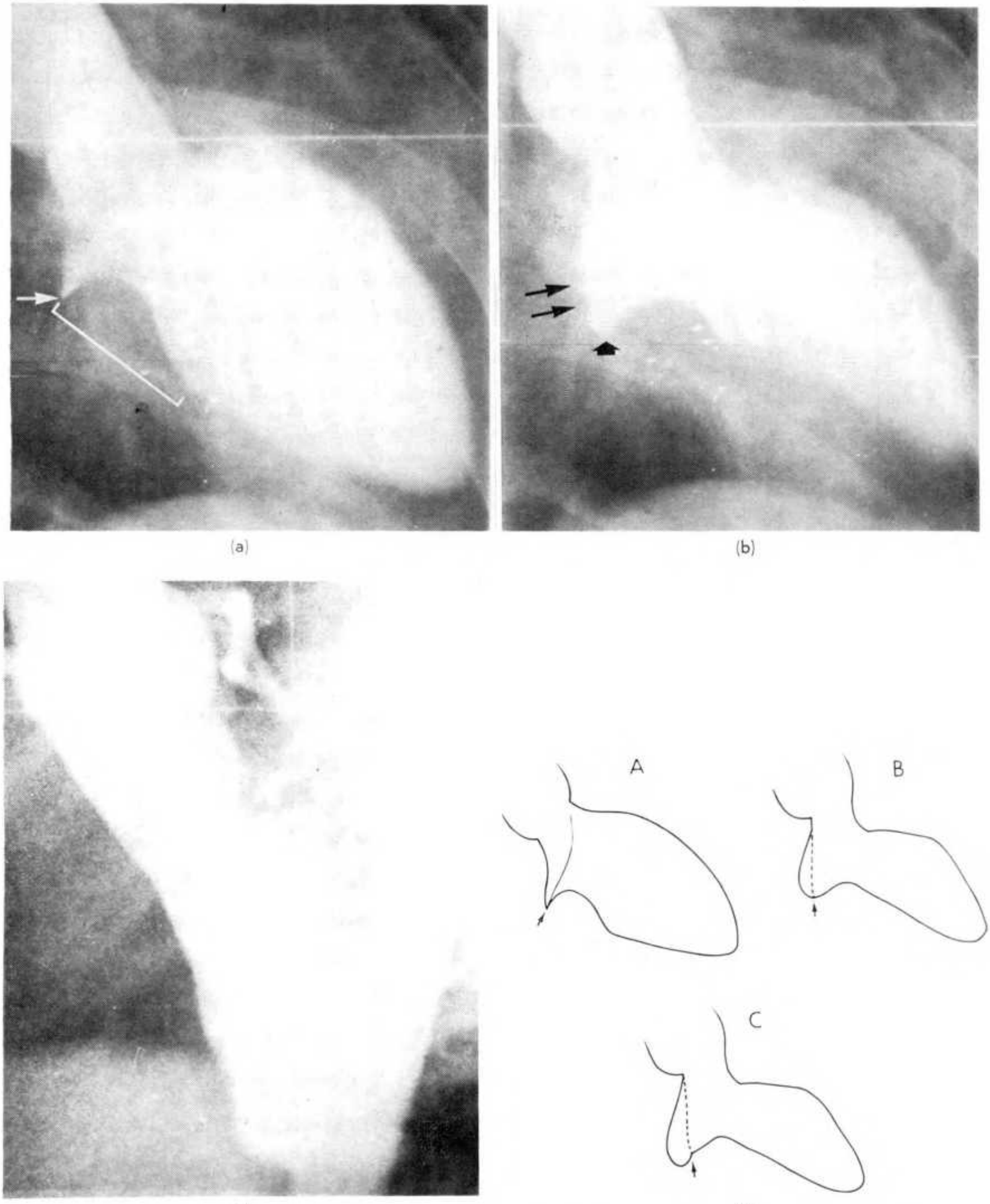
Fig. 3 *Components of the mitral valve apparatus (right anterior oblique projection).* (a) *The low lying fulcrum* (arrow) *and absence of notching of the left ventricular fornix* (white bracket) *in this diastolic frame make the mitral valve configuration type I. The upper margin of the fornix can be identified by the beak sign* (arrows). *pm, posterior papillary muscle.* (b) *During systole the posteromedial scallop* (long white arrows) *of the posterior mitral leaflet and posteromedial commissure (most superior linear lucency) are shown. The right margin of the outflow tract of the left ventricle formed by the atrioventricular septum is well delineated* (white arrow-heads). *Both papillary muscles are apparent (pm).*

mitral fulcrum with no notching of the fornix. In type IV there was a high mitral fulcrum and a notched left ventricular fornix. Types I and IV were seen in 39 and 38 cases, respectively; types II and III were seen in nine and 14 cases, respectively. The papillary muscles were seen in all patients in the right anterior oblique projection during systole and in the left anterior oblique projection during both systole and diastole. Chordae tendineae were clearly visible in the right anterior oblique projection in five cases during systole. The posteromedial commissure was seen in 50 cases. The posteromedial scallop was by far the most commonly identified component (32 cases) of the posterior mitral leaflet (Fig. 3). The middle and anterolateral scallops were seen in six cases. All three scallops of the posterior leaflet of the mitral valve were identified in four instances.

The mitral fulcrum was always identified in the right anterior oblique projection by contrast trapped in the recess between the leaflet and the adjacent endocardium (Fig. 1 and 3a). The line of attachment of the posterior mitral leaflet sharply outlined the width of the mitral valve ring in diastole (Fig. 1); the upper margin of the left ventricular fornix was distinctly seen and identified in systole and diastole as a dense beak (Fig. 1 and 3a). In 74 ventriculograms the diameter of the mitral ring on the right anterior oblique projection decreased by 2 to 23 per cent in systole; in 26 patients the diameter did not change. We were able to measure the diameter of the mitral valve ring in the left anterior oblique projection in six of the 26 patients who showed no change in the right anterior oblique projection: in two of them the diameter was unchanged, but in the other four it was less 5 to 14 per cent. In an additional 33 ventriculograms the diameter of the mitral ring could also be measured in the left anterior oblique projection; there was a reduction in diameter in systole up to 37 per cent, though there was no change in seven cases. The percentage change in mitral ring diameter from diastole to systole showed no correlation with the patient's age.

In 80 patients no bulging of mitral leaflets into the left atrium could be detected. In the remaining 20 patients (Fig. 4) the normal mitral valve pro-

Fig. 4 *Pseudoprolapse of the mitral valve.* (a) *Right anterior oblique projection. Early diastolic frame from left ventriculogram. The fulcrum is low lying* (arrow) *and the fornix is notched* (square bracket) *making this a type II mitral valve.* (b) *During systole there is normal bulging of the mitral leaflets* (long arrows), *but no posterior and inferior displacement beyond the fulcrum* (short wide arrow), *thus identifying this as a pseudoprolapse. An echocardiogram showed a normal mitral valve. Phonocardiography showed no mid-systolic click or late systolic murmur. It is essential to identify the fulcrum as a point of reference before making the diagnosis of prolapse of the mitral valve.* (c) *Left anterior oblique projection. No prolapse of the mitral valve is seen.* (d) *Panels A and B represent diastolic and systolic frames shown in Fig. 4a and b. The arrow indicates the fulcrum. The dotted line depicts the usual configuration of the mitral valve in systole. However, in some normal patients (20%) the mitral leaflet may bulge*



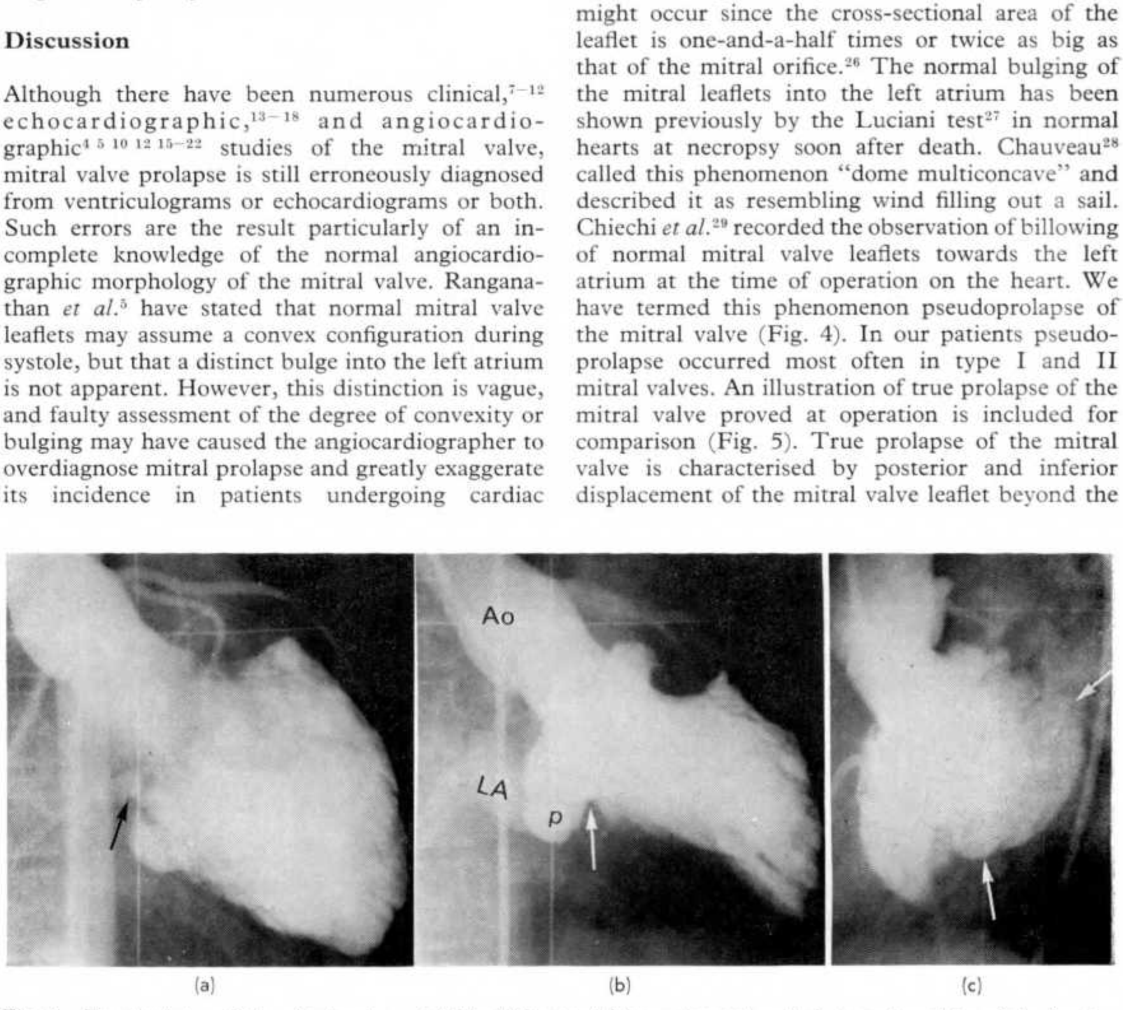
(a) (b) (c) (d)

in systole without posterior and inferior displacement beyond the fulcrum. In this patient (panel B) *only leaflet bulging was noted. If prolapse had been present, the silhouette depicted in panel C would have been recorded. In this sketch mitral leaflet bulges inferiorly and posteriorly to the fulcrum. The diagnosis of mitral valve prolapse depends on identification of the fulcrum on technically excellent angiocardiograms.*

truded from 3·5 to 6·5 mm (mean ± SEM 4·95 ± 0·2 mm) into the left atrium during systole. In no case was there any posterior and inferior para-annular displacement of the mitral valve leaflet beyond the level of the mitral valve fulcrum. No wall motion abnormalities were detected in any of these patients.[4 6] Echocardiograms and phonocardiograms showed no evidence of prolapse of the mitral valve and mid-systolic click or late systolic murmur. In these patients, failure to recognise the mitral fulcrum could have led to the incorrect diagnosis of prolapse of the mitral valve.

Discussion

Although there have been numerous clinical,[7-12] echocardiographic,[13-18] and angiocardiographic[4 5 10 12 15-22] studies of the mitral valve, mitral valve prolapse is still erroneously diagnosed from ventriculograms or echocardiograms or both. Such errors are the result particularly of an incomplete knowledge of the normal angiocardiographic morphology of the mitral valve. Ranganathan *et al.*[5] have stated that normal mitral valve leaflets may assume a convex configuration during systole, but that a distinct bulge into the left atrium is not apparent. However, this distinction is vague, and faulty assessment of the degree of convexity or bulging may have caused the angiocardiographer to overdiagnose mitral prolapse and greatly exaggerate its incidence in patients undergoing cardiac catheterisation.[23-25] Measurements on the patients reviewed here indicate that 20 per cent of normal people have mitral leaflets which bulge into the atrium during systole by less than 6·5 mm from the plane of the mitral valve. In none of these normal cases was there posterior and inferior displacement of the mitral valve leaflet beyond the level of the mitral valve fulcrum. The reports by Smith *et al.*,[23] Raizada *et al.*,[24] and Ruwitch *et al.*[25] document the frequent observation of end-systolic bulging of the mitral leaflets. It is not surprising that some degree of systolic mitral leaflet bulging might occur since the cross-sectional area of the leaflet is one-and-a-half times or twice as big as that of the mitral orifice.[26] The normal bulging of the mitral leaflets into the left atrium has been shown previously by the Luciani test[27] in normal hearts at necropsy soon after death. Chauveau[28] called this phenomenon "dome multiconcave" and described it as resembling wind filling out a sail. Chiechi *et al.*[29] recorded the observation of billowing of normal mitral valve leaflets towards the left atrium at the time of operation on the heart. We have termed this phenomenon pseudoprolapse of the mitral valve (Fig. 4). In our patients pseudoprolapse occurred most often in type I and II mitral valves. An illustration of true prolapse of the mitral valve proved at operation is included for comparison (Fig. 5). True prolapse of the mitral valve is characterised by posterior and inferior displacement of the mitral valve leaflet beyond the



(a) (b) (c)

Fig. 5 *True prolapse of the mitral valve.* (a) *The high mitral fulcrum* (arrow) *and absence of notching of the fornix in this diastolic frame make the mitral valve configuration type III.* (b) *During systole there is posterior and inferior displacement of the mitral valve tissue beyond the fulcrum* (arrow) *resulting in true prolapse (p) of the mitral valve. Very mild mitral regurgitation is shown. LA, left atrium.* (c) *A systolic frame in the left anterior oblique projection clearly shows para-annular displacement of the posterior leaflet of the mitral valve characteristic of true prolapse of the mitral valve* (arrows). *Simultaneous echocardiogram and phonocardiogram showed mitral valve prolapse and a mid-systolic click.*

level of the mitral valve fulcrum in the right anterior oblique projection. Systolic leaflet bulging is not sufficient to make the correct diagnosis of prolapsing mitral valve. Because of the low fulcrum in types I and II, the erroneous diagnosis of mitral prolapse is most likely to be made in these groups. Since the frequency of type I and II mitral valves is 39 and 9 per cent, respectively, the potential for the misdiagnosis of mitral valve prolapse is present in nearly 50 per cent of normal angiocardiograms. The recent work of Cohen *et al.*[30] using these criteria showed their accuracy in diagnosing mitral valve prolapse, with elimination of false positives.

Redundancy of the leaflets and/or elongation of the chordae tendineae, usually secondary to mucoid degeneration[31] (blue valve syndrome),[32] alters the line of coaptation of the mitral leaflets and produces prolapse of the mitral valve. During closure of the normal mitral valve, there is initially apposition of the edges of the leaflets with subsequent contact of their atrial surfaces. Progressive contraction of the myocardial fibres and increased intraventricular pressure cause traction on the chordae tendineae, further surface contact, and bulging of the cusps into the left atrium. The ratio of valvar tissue surface area to mitral orifice area required to produce closure is nearly two to one.[26 29] On transillumination the anterior and posterior mitral leaflets have three zones: basal, membranous (clear), and rough. The rough zone of the anterior and posterior leaflets forms the coaptation surface area, which is distinctly delineated by a ridge on the atrial aspect of the mitral leaflets. This ridge marks the line of leaflet closure and according to Ranganathan *et al.*[33] is 0·8 to 1·0 cm from the free margins of the leaflets. If the line of coaptation is disturbed but there is still partial contact of the coaptation leaflet surfaces, mitral prolapse is produced with no mitral regurgitation. If there is loss of coaptation, however, mitral regurgitation will ensue. The degree of mitral regurgitation will depend on the extent of mitral prolapse. Any degree of mitral prolapse with or without mitral regurgitation can be detected on angiocardiography as long as the fulcrum and the type of mitral valve are identified in early diastole in the right anterior oblique projection.

With the advent of caesium iodide intensifiers and their increasing use in angiocardiography, it is important to recognise the normal anatomy of the mitral valve in the right anterior oblique projection if errors in diagnosis are to be avoided. This is particularly true of the posterior leaflet of the mitral valve, which is in most cases a tri-scalloped structure.[29 33] The posteromedial commissure and posteromedial scallop are by far the most commonly identified components of the mitral valve during ventriculography. It is important to differentiate these normal scallops from the cleft anterior mitral leaflet found in endocardial cushion defects.

In 26 per cent of patients with normal mitral valves and ventricles without annular calcification, contraction of the ventricle failed to reduce the diameter of the mitral valve annulus in the right anterior oblique projection. This observation indicates that the sphincter-like action of the annulus[34] plays only a secondary role in the mechanism of mitral valve closure. Our studies did not support See[35] and Harken *et al.*[36] who contend that the anterior leaflet of the mitral valve acts like a curtain extending across the mitral orifice (which remains entirely hidden) and that the posterolateral wall moves in and buttresses the posterior leaflet. No correlation could be identified between the degree of mitral annular shortening and age of the patient.

References

[1] Seldinger SI. Catheter replacement of the needle in percutaneous arteriography—a new technique. *Acta Radiol* 1953; **39:** 368–76.

[2] Judkins MP. Percutaneous transfemoral selective coronary arteriography. *Radiol Clin North Am* 1968; **6:** 467–92.

[3] Judkins MP. Selective coronary arteriography: I. A percutaneous transfemoral technic. *Radiology* 1967; **89:** 815–24.

[4] Ranganathan N, Silver MD, Robinson TI, Wilson JK. Idiopathic prolapsed mitral leaflet syndrome: angiographic-clinical correlations. *Circulation* 1976; **54:** 707–16.

[5] Ranganathan N, Silver MD, Robinson TI, *et al.* Angiographic-morphologic correlation in patients with severe mitral regurgitation due to prolapse of the posterior mitral valve leaflet. *Circulation* 1973; **48:** 514–8.

[6] Ruttley MS, Adams DF, Cohn PF, Abrams HL. Shape and volume changes during "isovolumetric relaxation" in normal and asynergic ventricles. *Circulation* 1974; **50:** 306–16.

[7] Barlow JB, Pocock WA, Marchand P, Denny M. The significance of late systolic murmurs. *Am Heart J* 1963; **66:** 443–52.

[8] Barlow JB, Bosman CK. Aneurysmal protrusion of the posterior leaflet of the mitral valve: an auscultatory-electrocardiographic syndrome. *Am Heart J* 1966; **71:** 166–78.

[9] Hancock EW, Cohn K. The syndrome associated with midsystolic click and late systolic murmur. *Am J Med* 1966; **41:** 183–96.

[10] Barlow JB, Bosman CK, Pocock WA, Marchand P. Late systolic murmurs and non-ejection ("mid-late") systolic clocks: an analysis of 90 patients. *Br Heart J* 1968; **30:** 203–18.

[11] Jeresaty RM. The syndrome associated with mid-systolic click and/or late systolic murmur: analysis of 32 cases. *Chest* 1971; **59:** 643–7.

[12] Jeresaty RM. Mitral valve prolapse-click syndrome. *Prog Cardiovasc Dis* 1973; **15:** 623–52.

[13] Dillon JC, Haine CL, Chang S, Feigenbaum H. Use of echocardiography in patients with prolapsed mitral valve. *Circulation* 1971; **43:** 503–7.

[14] Kerber RE, Isaeff DM, Hancock EW. Echocardiographic patterns in patients with the syndrome of systolic click and late systolic murmur. *N Engl J Med* 1971; **284:** 691–3.

[15] DeMarie AN, King JF, Bogren HG, Lies JE, Mason DT. The variable spectrum of echocardiographic manifestations of the mitral valve prolapse syndrome. *Circulation* 1974; **50:** 33–41.

[16] Sahn DJ, Allen HD, Goldberg SJ, Friedman WF. Mitral valve prolapse in children: a problem defined by real-time cross-sectional echocardiography. *Circulation* 1976; **53:** 651–7.

[17] Gilbert BW, Schatz RA, VonRamm OT, Behan VS, Kisslo JA. Mitral valve prolapse: two-dimensional echocardiographic and angiographic correlation. *Circulation* 1976; **54:** 716–23.

[18] Markiewicz W, Stoner J, London E, Hunt SA, Popp RL. Mitral valve prolapse in one hundred presumably healthy young females. *Circulation* 1976; **53:** 464–73.

[19] Criley JM, Lewis KB, Humphries JO, Ross RS. Prolapse of the mitral valve: clinical and cine-angiographic findings. *Br Heart J* 1966; **28:** 488–96.

[20] Stannard M, Sloman JG, Hare WSC, Coble AJ. Prolapse of the posterior leaflet of the mitral valve: a clinical, familial, and cineangiographic study. *Br Med J* 1967; **3:** 71–4.

[21] Kittredge RD, Shimomura S, Cameron A, Bell ALL Jr. Prolapsing mitral valve leaflets: cineangiographic demonstration. *Am J Roentgenol* 1970; **109:** 84–93.

[22] Jeresaty RM. Ballooning of the mitral valve leaflets: angiographic study of 24 patients. *Radiology* 1971; **100:** 45–52.

[23] Smith ER, Fraser DB, Purdy JW, Anderson RN. angiographic diagnosis of mitral valve prolapse: correlation with echocardiography. *Am J Cardiol* 1977; **40:** 165–70.

[24] Raizada V, Benchimol A, Desser KB, Reich FD, Sheasby C, Graves C. Mitral valve prolapse in patients with coronary artery disease: echocardiographic-angiographic correlation. *Br Heart J* 1977; **39:** 53–60.

[25] Ruwitch JF Jr, Weiss AN, Fleg JL, McKnight RC, Ludbrook PA. Insensitivity of echocardiography in detecting mitral valve prolapse in older patients with chest pain. *Am J Cardiol* 1977; **40:** 686–90.

[26] Brock RC. The surgical and pathological anatomy of the mitral valve. *Br Heart J* 1952; **14:** 489–513.

[27] Luciani L. La meccanica del cuore. In: *Fisiologia dell'uomo*. Milano: Soc Ed Lib, 1901: 156–206.

[28] Chauveau MM, Arloing : Coeur (physiologie). In: *Dictionnaire encyclopédique des sciences médicales*. Tome XVIII. Paris: 1876: 314–82.

[29] Chiechi MA, Lees WM, Thompson R. Functional anatomy of the normal mitral valve. *J Thorac Surg* 1956; **32:** 378–98.

[30] Cohen MV, Shah PK, Spindola-Franco H. Angiographic-echocardiographic correlation in mitral valve prolapse. *Am Heart J* 1979; **97:** 43–52.

[31] Fernex M, Fernex C. La dégénérescence mucoïde des valvules mitrales. *Helv Med Acta* 1958; **25:** 694–705.

[32] McCarthy L, Wolf PL. Mucoid degeneration of heart valves: "blue valve syndrome" (abstract). *Am J Cardiol* 1970; **25:** 115.

[33] Ranganathan N, Lam JCH, Wigle ED, Silver MD. Morphology of the human mitral valve. II. The valve leaflets. *Circulation* 1970; **41:** 459–67.

[34] Smith HL, Essex HE, Baldes EJ. A study of the movements of heart valves and of heart sounds. *Ann Intern Med* 1950; **33:** 1357–9.

[35] See M-D. *Recherches sur l'anatomie et la physiologie du coeur*. Paris: Masson, 1875.

[36] Harken DE, Ellis LB, Ware PF, Norman LR. The surgical treatment of mitral stenosis, valvuloplasty. *N Engl J Med* 1948; **239:** 801–9.

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Variations in height of jugular "a" wave in relation to heart rate in normal subjects and in patients with atrial septal defect

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SUMMARY Analysis of jugular tracings in seven normal subjects in sinus rhythm whose heart rate varied spontaneously from one moment to another during expiratory apnoea, showed that a pronounced variation occurred in the size of the "a" waves in relation to that of the "v" waves and in accordance with the corresponding RR interval. In the 53 measurements which were carried out, the "a/v" ratio had a mean value of 0·9 for a heart rate above 87, 1·4 for a heart rate between 87 and 68, and 1·1 for a heart rate less than 68. The variations in the size of the "a" waves in relation to heart rate are explained by the place of atrial systole during the different phases of ventricular filling.

This variation in the height of the "a" wave has also been found in patients with an atrial septal defect for heart rates between 62 and 86, and this could lead to misdiagnosis, either dimissing the diagnosis of atrial septal defect when the heart rate is around these values, or suspecting it wrongly when the heart rate is either slower or faster.

When examining jugular tracings, one should therefore be cautious about interpreting the size of the "a" wave which should be evaluated as a function of heart rate.

Measurement of the height of the "a" wave, which reflects right atrial systole, is one of the features which is essential for study of the jugular venous pulse. It is considered in relation to the height of the "v" wave, and it is usual to regard the height of the normal "a" wave to be between one and one-and-a-half times that of the "v" wave.[1 2] If it is above this value, one can presume an increase in pressure in the right atrium caused by an obstruction to the outflow. Below this limit it would suggest over-distension of the right atrium such as is seen, for example, in atrial septal defects.

In practice, the "a/v" ratio varies with the heart rate,[3] a fact which has been appreciated only by few authors until now and the aim of the present study is to show, by observations on subjects with normal hearts, that the height of the "a" wave varies in relation to the heart rate and this notion finds an application in patients with an atrial septal defect.

Subjects and methods

NORMAL SUBJECTS

The reason for investigating these seven normal subjects was the presence of a systolic murmur, the clinical features of which suggested that the heart was normal. These cases were selected because they were in sinus rhythm, with a heart rate which varied from one moment to another, even during a period of strict expiratory apnoea. The electrocardiogram was normal and sinus rhythm was confirmed by the constancy of the P waves, the PR intervals, and the ventricular complexes throughout the tracings, only the RR interval varying from one time to another.

All seven subjects were young, with a mean age of 21 (range: 15 to 35 years), three were female and four were male. The absence of an underlying cardiac lesion was first established on clinical, radiological, and electrocardiographic evidence, and confirmed in all cases by a complete phonomechanocardiographic study based on recordings of the phonocardiogram from different praecordial positions and of the jugular, carotid, and apical tracings. The carotid study was done at rest and repeated during a pharmacodynamic test with isoprenaline and with methoxamine. In one patient (case 4) haemodynamic and angiographic investigations were also carried out.

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ATRIAL SEPTAL DEFECT

Two groups of patients suffering from atrial septal defect confirmed by haemodynamic investigation were selected for this study. The first group of four patients was especially interesting because of the spontaneous variations in heart rate from one systole to another in the same subject during expiratory apnoea, though the P waves, PR intervals, and ventricular complexes were exactly the same. Ninety-nine "a/v" ratios were measured. The findings in these four patients were similar to those of seven normal subjects with a spontaneously variable heart rate studied previously. The second group of 38 patients had a stable heart rate varying from 58 to 120.

Excluded from this study were cases of atrial septal defect with increased pulmonary pressure and those that were too small to show an increase in the pulmonary output/systemic output ratio.

METHODOLOGY

The recordings were made with an eight-channel Thomson-Telco apparatus with photographic recordings at 50 mm/s and with a piezoelectric venous pulse Hellige recorder. In addition to the venous pulse, an electrocardiogram (lead II), and a phonocardiogram at three frequencies (high, medium, and low) at the apex and the third left intercostal space, were recorded simultaneously.

All recordings were made during an unforced respiratory apnoea.

Such an expiratory apnoea, a simple pause during a normal respiratory cycle, gives us a stabilisation of the jugular tracing (Fig. 1). It has been verified, in the course of catheterisation procedures on the heart that such an unforced expiratory apnoea of 10 to 12 seconds' duration does not change the haemodynamic status of the right atrium. The value of the mean right atrial pressures and the mean value of each of the "a" and "x" waves and "v" depression measured during a normal respiratory cycle remain identical to those measured during the first 6 to 8 seconds of the expiratory apnoea; after they decrease slightly by 1 or 2 mmHg, the ratios of the "a" and "x" waves and "v" depression remain unchanged.

Measurements were taken on the height of the "a" and "v" waves from their departure from the horizontal to the lowest point on the curve to determine the "x" depression (Fig. 2). The value of the "a" wave was established in relation to the "v" wave and expressed as an "a/v" ratio. At the same time, the corresponding RR interval in hundredths of a second was determined.

Results and comments

NORMAL SUBJECTS

Results

Fifty-three measurements of the "a/v" ratio in relation to the RR intervals were measured, and are shown in Fig. 3.

The RR intervals varied with the patient and with the sections of tracings studied from 0·59 to 0·99 s, corresponding to a heart rate of 102 to 61. For the same subject the variations in the RR intervals were more important, for an increase of 60 per cent in comparison with the basic value could be seen.

The height of the "a" wave expressed as an "a/v" ratio varied between 0·6 to 2·4. The variations in wave height in the same subject could differ very considerably, up to 240 per cent of the basic value.

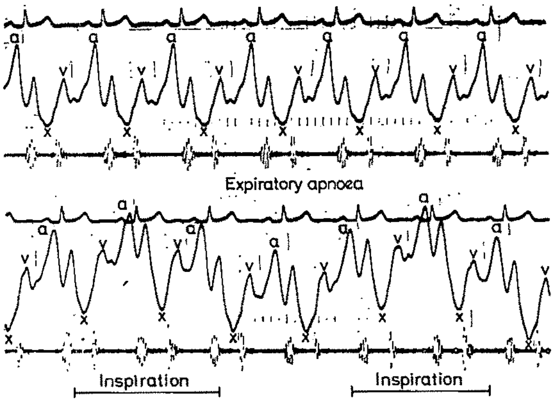


Fig. 1 *Jugular tracing recorded during unforced expiratory apnoea* (top) *and during normal respiration.*

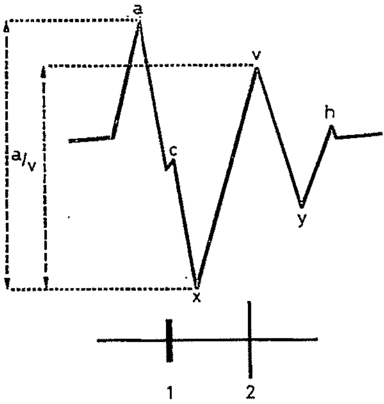


Fig. 2 *Method of calculation of the "a/v" ratio.*

If one regards the normal "a/v" ratio values to lie between 1 and 1·5, then 29 of the 53 measurements done were within normal limits (Fig. 3, shaded area) and there were 13 values below and 11 above these limits. The "a" wave values which fall within the accepted normal limits, that is between 1 and 1·5, could be seen at all heart rates. In the seven subjects studied, the RR interval ranged from 0·59 to 0·97 (heart rate of 102 to 62). For the 11 readings which were above 1·5, indicating abnormally large "a" waves, the RR intervals ranged from 0·69 to 0·88 s (heart rate of 87 to 68), except in one subject in whom the RR interval was 0·93. In the 13 cases in whom the "a/v" ratio was below 1, basically indicating small "a" waves, the RR intervals were either below 0·69 (heart rate above 87), or above 0·88 (heart rate below 68) except in three cases where the values were 0·70, 0·74, and 0·87.

One can therefore classify the "a" waves into three groups according to their height in relation to the RR intervals.

Type "1": The RR interval was below 0·69 (heart rate over 87). There were five "a" waves in this group which corresponded to an "a/v" ratio of less than 1 (and, therefore, unduly small) and three to a ratio of 1 to 1·5 (normal). The mean value of the "a/v" ratio for these five "a" waves was 0·9 (limits 0·6 to 1·2).

Type "2": The RR interval lay between 0·69 and 0·88 (heart rate between 87 and 68). There were 33 "a" waves in this group, 10 corresponding to an "a/v" ratio of more than 1·5 (therefore abnormally large), in 20 the ratio was between 1 and 1·5 (normal), and in only three was the ratio below 1 (abnormally small). The mean value of the 33 "a/v" ratios was 1·4 (limits 0·8 to 2·4).

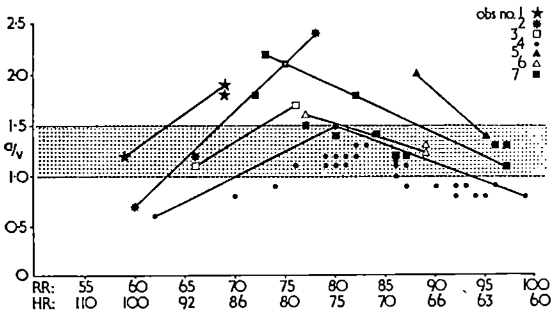


Fig. 3 *Progression in the size of the "a" wave ("a/v" ratio) in relation to the corresponding RR interval in hundredths of a second, and to the heart rate (HR) in seven subjects. The end-points of this progression come together on the right-hand side. Note that in case 4 the pronounced variability in the RR interval allows the "a" wave to pass through the three different sizes. Shaded area is where the "a/v" ratio is usually regarded as normal.*

Type "3": The RR interval was above 0·88 (heart rate below 68). There were 15 "a" waves in this group, of which eight corresponded to an "a/v" ratio of less than one (and therefore small), in six the ratio laid between 1 and 1·5 (normal), and in one case the ratio was above 1·5 (therefore large). The mean value of "a/v" was 1·1 (limits: 0·8 to 1·9).

In summary, the "a" waves regarded as normal in size, that is with an "a/v" ratio of between 1 and 1·5, occurred at all heart rates, the smaller waves ("a/v" ratio below 1) were only seen when the heart rate was either fast or slow, and the larger waves ("a/v" ratio above 1·5) only for the middle range of heart rates.

Two subjects merit detailed discussion.

Case 4 (Fig. 4) showed all three types and had a very variable heart rate from 97 to 61 (RR intervals of 0·62 to 0·99). Accordingly, the height of the "a" wave in this subject was very variable and represented all three types: 1, 2, and 3 according to whether the heart rate was fast, medium, or slow, with several intermediate values. This case showed in the same subject all the possible variations in the "a/v" ratio in relation to the heart rate, variations which were seen only incompletely in the other six subjects. In this subject one could recognise the division of the "a/v" ratios into three groups according to the values of the RR interval, one value of 0·6 for type 1, 18 (mean values 1·1) for type 2, and eight (mean value 0·8) for type 3. There was no overlap or separate divisions for the "a/v" values in relation to the RR intervals in the 27 "a/v" ratios measured, except for four values. For one RR interval of 0·87, two values differing slightly in their "a/v" ratio were equal to 0·9 to 1·1. For one RR interval at 0·70, the ratio was equal to 0·8, and for the fourth RR interval at 0·74, the ratio was 0·9.

The second patient was unusual for the pronounced variations in the size of the "a" waves in relation to relatively minor changes in the heart rate. Even when the RR interval went from 0·60 to 0·78, an increase of 30 per cent (heart rate from 100 to 77), the "a/v" ratio changed from 0·7 to 2·4, an increase of 240 per cent.

Comments

The facts given above contradict the accepted view that the size of the "a" wave is abnormal when, expressed as the "a/v" ratio, it is above 1·5 or below 1. In fact, the "a/v" ratio varies considerably with the heart rate as can be seen in the seven subjects recorded above in whom the heart rate changed spontaneously from one moment to another, though the electrocardiographic complexes remained exactly the same and the measurements were recorded during strict expiratory apnoea.

The "a/v" ratio had a mean value of 0·9 when the RR intervals were less than 0·69 and a mean value of 0·62, which corresponds to a rapid heart rate of more than 87 (mean 97).

The "a/v" interval is greater, with a value of 1·4, when the RR interval lies between 0·69 and 0·88 (mean 0·80) which corresponds to a heart rate between 87 and 68 (mean 75). Lastly, the "a/v" ratio is smaller (mean 1·1) when the RR interval is prolonged and above 0·88 (mean 0·94) which corresponds to a heart rate below 68 (mean 64). It should be noted that though there could be some overlap in the "a/v" values from one subject to another, there was none in the same subject (except slightly for two values in case 4). It should also be emphasised that the cut-off points for heart rate (fast: over 87; medium: between 68 and 87; slow: below 68), which have determined the classification of the "a" wave into three groups cannot be considered as strict values since we are dealing with only seven normal subjects.

The size of the "a" wave in relation to the "v" wave ought then to be interpreted with caution on jugular tracings as the "a/v" ratio can vary considerably with the duration of the RR interval, that is it follows the heart rate. The concept of a larger "a" wave should be interpreted with caution when the RR interval lies between 0·69 and 0·88 (heart rate 87 and 68), since an "a/v" ratio of more than 1·5 can be seen in normal subjects.

An "a/v" ratio of more than 1·5 does not necessarily represent an increased right atrial pressure if the heart rate lies between 68 and 87. In the same way, a small "a" wave, giving an "a/v" ratio of less than 1, should not necessarily suggest distension of the right atrium such as one sees in atrial septal defects, since an "a/v" ratio of less than 1 can be seen in normal subjects when the RR interval is below 0·69 (heart rate above 87) or above 0 88 (heart rate below 68).

The variations in the height of the "a" wave seem to depend mainly on the time when atrial systole takes place in relation to the different stages of ventricular filling (Fig. 5). When the heart rate is rapid (and the RR interval is short, below 0·69), atrial contraction takes place early, soon after the opening of the tricuspid valve, and the amount of blood discharged during atrial systole is to some

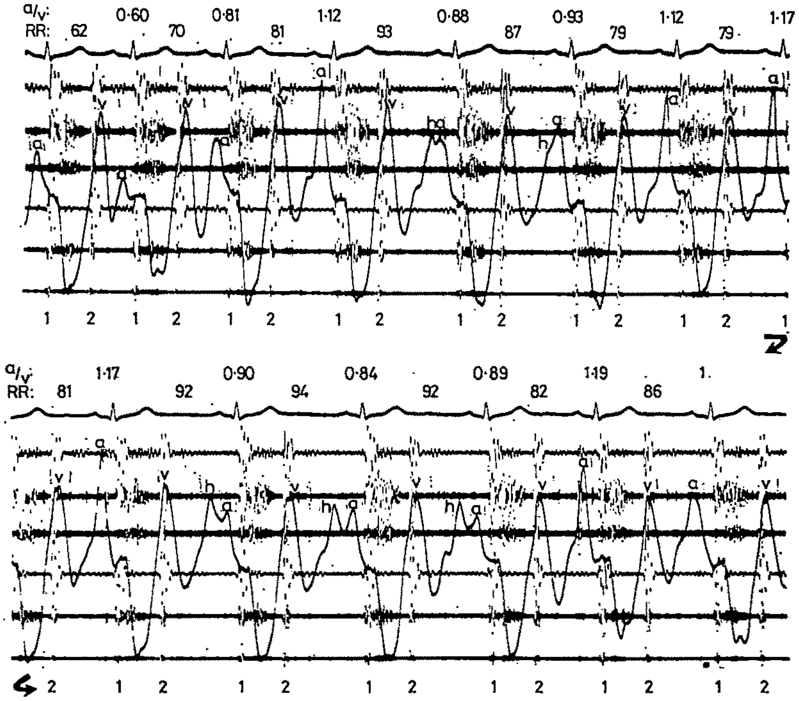


Fig. 4 *Extract from a continuous jugular tracing in a normal subject (case 4) in expiratory apnoea. From above downwards: a standard electrocardiograph lead II, the first phonocardiogram at three frequencies (low, medium, and high) parasternally in the third left intercostal space, and, below, another phonocardiogram with the same frequencies at the apex area. "a/v", ratio of the size of the "a" wave in relation to that of the "v" wave; RR, RR intervals in hundredths of a second. Recording speed of the paper was 50 mm/s.*

extent drawn by ventricular suction through the valve which is fully open. Atrial contraction cannot then cause an increase in atrial pressure. This explains why the "a" wave may be rather small on the jugular tracing and this takes place when the curve descends from "v" towards "y". When the heart rate is a little slower (RR interval between 0·69 to 0·88) atrial systole occurs during the rapid filling of the ventricle when the free borders of the valves are coming together. Atrial systole thus comes up against an obstacle on which it impacts and this causes a rise in the atrial pressure which shows itself as a larger "a" wave on the jugular tracing, and higher than the "v" wave. Finally, when the heart rate is slow (RR interval above 0·88) atrial systole occurs during slow ventricular filling and stasis, that is the phase when the valves have just opened and the ventricle can easily receive the contents of the atrium. Atrial contraction does not then lead to any appreciable rise in pressure and the "a" wave on the jugular tracing remains smaller than in the previous situation.

Variations in "a" wave size therefore respond to a physiological situation and this fact should be borne in mind when interpreting jugular tracings.

ATRIAL SEPTAL DEFECT

The diagnosis of atrial septal defect on the jugular pulse tracing is suggested when the "v" wave is higher than the "a" wave, which indicates an increase in right atrial filling caused by left-to-right atrial shunt, whereas normally the "v" wave amplitude is less than that of the "a" wave.

Results

As in normal subjects, it seems that the amplitude of the "a" wave varies considerably with the heart rate and Fig. 6 shows a striking similarity to the curves seen in the previously studied normal subjects.

(a) In those with a rapid heart rate (RR interval below or equal to 0·70), the "a/v" ratio was usually below 1, and in no case was it above 1·5 (type 1 "a" waves).

(b) In those with a medium heart rate (RR interval between 0·71 and 0·96) the amplitude of the "a" wave was increased and the "a/v" ratio was generally above 1·5, and in all cases it was above 1 (type 2 "a" waves) except in two cases whose heart rate approached that of the following group.

(c) In those with a slow heart rate (RR interval above 0·96) the amplitude of the "a" waves was further diminished and the "a/v" ratio was below 1·5 or even below 1 (type 3 "a" waves).

The line of demarcation between the three zones is definite between the first two (RR=0·70), less clear-cut with a heart rate a little slower than in normal subjects between the last two (RR > 0·96).

One interesting fact is that the "a/v" ratio is always above or equal to 1 for heart rates which

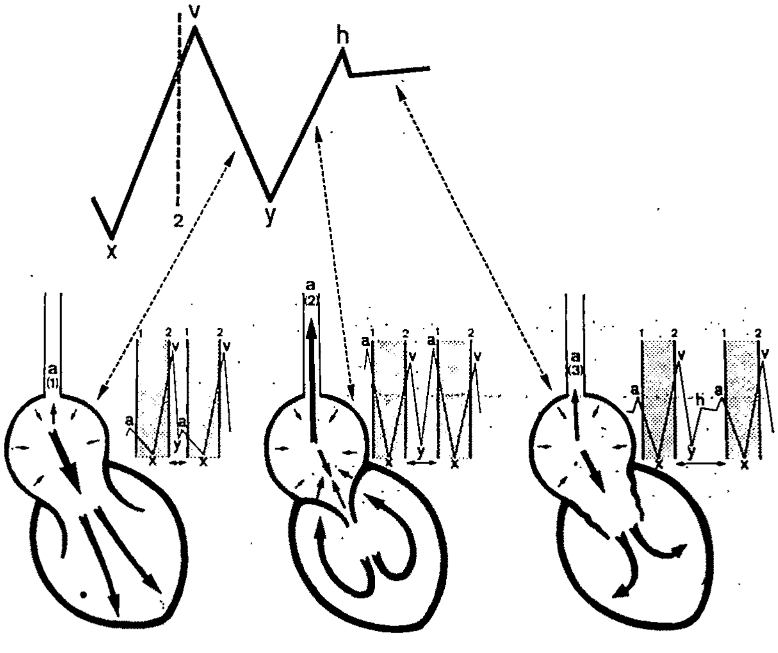


Fig. 5 *Plan showing the three types of jugular tracing according to whether the "a" waves appear early or later during diastole.* Above: *the terminal point of a normal jugular vein tracing with the appearance of "x", "v", "y", and "h" and the second sound (2).* Below: *from left to right, the progressively later appearance of the "a" wave during diastole, either between "v" and "y" (=a1), or between "y" and "h" (=a2), or after "h" (=a3) (see text for comments).*

would be considered as normal, above 60 and below 85. The presence of very large "a" waves (above or equal to two "v") can even be seen in this zone but they are very unusual in cases of atrial septal defect without pulmonary hypertension.

Among the four cases of atrial septal defect with a spontaneously variable heart rate, there were three (cases 1, 2, and 3) who presented with type 1 "a" waves smaller than the "v" waves, and changed to type 2 "a" waves, larger than the "v" waves, when the heart rate fell below 85 (RR > 0·70), thus confirming the course of events noticed in the previous 38 cases. Fig. 7 is a striking example of this. The fourth patient (Fig. 6, case 4) had the advantage of showing the three possibilities together and summarising in one patient the general course of the "a/v" ratio in relation to the heart rate. This course of events recalls that seen in subjects at a fixed heart rate (Fig. 3) and that seen in normal subjects. Fig. 8 shows 87 "a/v" ratios which were taken during the same recording in this subject during a course of repeated expiratory apnoea.

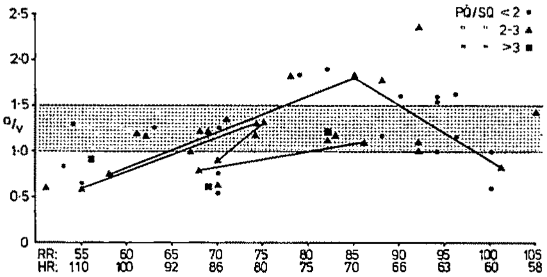


Fig. 6 *The "a/v" ratio of the jugular venous tracings (on the ordinate) in relation to the RR interval in hundredths of a second or heart rate (HR) (on the abscissa). The shaded area is that inside which the "a/v" ratio can be considered as normal, the area below is that in which the "a/v" ratio is less than 1, that is the area where this ratio is usually considered diagnostic of atrial septal defect. A line has been drawn joining the limits of the heart rates in four patients with atrial septal defect who had spontaneously variable heart rates. The points (pulmonary to systemic output ratio <2), the triangles (ratio between 2 and 3 included), and the squares (output ratio >3) refer to the 38 patients with a constant heart rate (see text for explanation).*

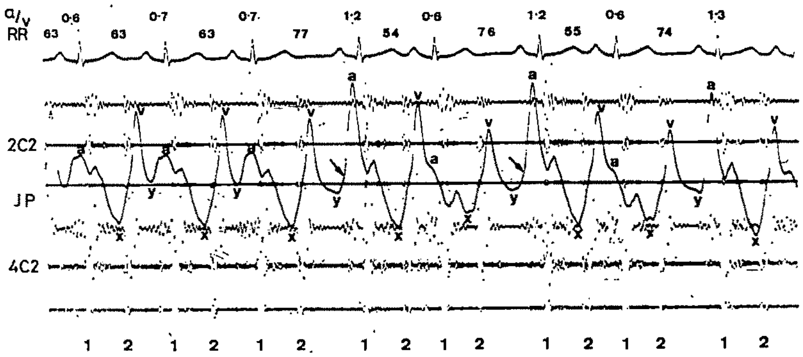
Comments

As in normal subjects, the height of the "a" wave is related to the heart rate and the same general comments apply to patients with atrial septal defect. However, there are small differences regarding heart rates at which the variations in the height of the "a" wave occur.

The "a" wave becomes abnormally tall (type 2) for medium-range heart rates with an RR interval between 0·71 and 0·96 (instead of 0·69 and 0·88 for normal subjects).

It becomes smaller, either for fast heart rates (type 1) with an RR interval equal to or below 0·70 (instead of 0·69 for normal subjects) or for slow heart rates (type 3) with an RR interval above 0·96 (instead of 0·88 for normal subjects).

These small differences between normal subjects and those with atrial septal defect could in fact be the result of the relatively small number of normal subjects studied. However, the overall evolution of the height of the "a" wave in atrial septal defect



a/v 0·6 0·7 0·7 1·2 0·6 1·2 0·6 1·3
RR 63 63 63 77 54 76 55 74
a
a
a
v
2C2
a
x
y
JP
4C2
1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2

Fig. 7 *Part of a jugular pulse and phonocardiogram tracing of a patient with atrial septal defect with a spontaneously variable heart rate. From above downwards: "a/v", ratio of the respective heights of the "a" and "v" waves; RR, RR interval in hundredths of a second; standard electrocardiograph lead II; the first part of a phonocardiogram recording with three frequency bands: low, medium, and high at the internal extremity of the second left intercostal interspace; the jugular pulse (JP) with the "a", "x", "v", and "y" waves. The arrows indicate the base of the "a" wave which is not clearly visible; a second phonocardiogram recording at the same frequencies as above, taken at the internal extremity of the fourth left intercostal interspace (1, 2: first and second heart sounds). See text for details.*

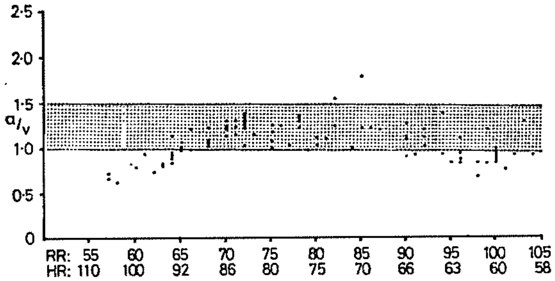


Fig. 8 *The "a/v" ratio on the jugular venous tracings on the ordinate, in relation to the RR interval or heart rate on the abscissa. The shaded area is that inside which the "a/v" ratio can be considered normal, the area below is that where the "a/v" ratio is < 1, that is where the ratio would generally be regarded as diagnostic of atrial septal defect. The points represent 87 "a/v" ratios measured in the same patient during several consecutive recordings in expiratory apnoea. The extreme limits of the "a/v" ratios in this patient are shown in Fig. 3 and are joined by an interrupted line (see text for explanation).*

is of the same type as that of normal subjects and is explained by the same physiological mechanisms.

On the other hand, the size of the shunt does not appear to influence the distribution of the "a" waves according to their amplitude in relation to those of the "v" waves, as is shown in Fig. 6. It seems reasonable to expect that cases of atrial septal defect with a large shunt would have an inversion of the "a/v" ratio and, conversely, in those cases of atrial septal defect with a low output, but this is not the case. Some patients with atrial septal defect with a pulmonary output to systemic ratio of more than 2 show larger type 2 "a" waves, larger than the "v" waves and vice versa. However, the mean pulmonary to systemic output ratio showed some correlation with the "a/v" ratio. The mean output ratio was 2·33 when this ratio was below 1, 2·22 when it lay between 1 and 1·5, and 1·92 when it was above 1·5. It, therefore, seems that when the output ratio decreases, the amplitude of the "a" waves exceeds that of the "v" waves and vice versa, though this correlation is not statistically significant.

We conclude that the presence of an atrial septal defect, even with an important shunt does not prevent the height of the "a" wave from being related to the heart rate as in normal subjects, a fact that has to be taken into consideration in diagnosing atrial septal defect.

Conclusion

The shape of the jugular venous pulse tracing in normal subjects and in patients with an atrial septal defect should be interpreted with caution as the height of the "a" wave varies according to the length of the preceding RR interval, that is the heart rate. For heart rates of 65 to 90 (in this study, 68 to 88 for normal subjects and 62 to 86 for atrial septal defect), the height of the "a" wave is often artificially increased. In normal subjects this could lead to the erroneous conclusion that the right heart pressures are raised. Conversely, in patients with atrial septal defect, this diagnosis could be wrongly dismissed. At a heart rate of below 65 and above 90, the diagnosis of atrial septal defect may be suspected erroneously in a normal subject because the height of the "a" wave could be artificially small as compared with the "v" wave.

For practical purposes the diagnosis of atrial septal defect based on phonomecanocardiographic data should not be automatically dismissed when the "a" wave is larger than the "v" wave, as this can occur in patients with atrial septal defect when the heart rate is between 65 and 90, and it should not automatically be made when the "a" wave is smaller than the "v" wave, for this can happen in normal subjects when the heart rate is either fast or slow.

References

1 Baragan J, Fernandez F. Renseignements hémodynamiques fournis par les enregistrements phonomécanocardiographiques externes. *Rev Prat* 1972; **22:** 1143–68.
2 Tavel ME. *Clinical phonocardiography and external pulse recording.* Chicago: Yearbook Medical Publishers, 1972: pp 52, 209.
3 Hartman H. The jugular venous tracing. *Am Heart J* 1960; **59:** 698–717.

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Subacute effusive constrictive epicarditis

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SUMMARY The coexistence of subacute pericardial effusion and epicardial constriction produces a clinical state, subacute effusive constrictive epicarditis, which resembles pericardial effusion with tamponade. However, pericardiocentesis results in only partial and temporary relief, a feature which is of importance in diagnosis. This syndrome was seen in five patients all of whom benefited from early pericardiectomy.

The acute and subacute phases of pericardial effusion may cause cardiac embarrassment by tamponade which, when relieved, results in a rapid restoration of normal ventricular filling.[1] The coexistence of acute or subacute pericardial effusion and constrictive epicarditis is unusual. First described from the Mayo Clinic by Burchell[2] and Edwards,[3] it was later recorded in patients with tuberculosis,[4] with uraemia,[5] after trauma,[6] after radiation,[7] with neoplastic involvement of pericardium,[8] with acute pyogenic pericarditis,[9–11] and with viral pericarditis.[12] Hancock[13] described the physiological alterations in detail and emphasised the diagnostic importance of combined cardiac catheterisation and pericardiocentesis. The paucity of reported cases suggests that the syndrome is uncommon. We have recently seen five cases in seven months and present them to record the

Table *Clinical data in five patients with subacute effusive constrictive epicarditis*

Case no.	*Age (y) sex*	*Presenting symptoms and duration*	*Pulse rate (beats/min) and blood pressure (mmHg)*	*Jugular venous pressure*	*Ankle oedema*	*Abdomen*	*Heart sounds*	*Pulsus paradoxus*	*Kussmaul's sign*	*Chest x-ray*
1	16 M	Dyspnoea, abdominal distension 1 year	88 100/80	Normal	++	Ascites, liver 10 cm, spleen 4 cm	Normal, no 3rd sound	0	0	Enlarged cardiac shadow
2	25 M	Fever, dyspnoea, left chest pain 6 wk	88 90/60	Raised	0	Liver 4 cm	Muffled heart sounds, no 3rd sound	0	0	Enlarged cardiac shadow, left pleural effusion
3	45 M	Fever, dyspnoea 12 wk	84 90/60	Raised, y descent	0	Liver 2 cm	Muffled heart sounds, no 3rd sound	0	+	Enlarged cardiac shadow, pericardial calcification +
4	17 F	Fever, cough, orthopnoea, chest pain 4 wk	120 120/70	Raised, y descent	+++	Liver 4 cm	Quiet heart sounds, no 3rd sound	0	0	Enlarged cardiac shadow
5	21 F	Fever, central chest pain, orthopnoea 2 wk	120 105/70	Raised	0	Normal	Normal heart sounds, pericardial rub	0	0	Enlarged cardiac shadow

PP, parietal pericardium; epi, epicardium. *Serological studies consistent with a viral infection.

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beneficial effects of early pericardiectomy.

Patients and methods

During the seven-month period between July 1976 and January 1977, five patients were admitted to the Thoracic Unit, Colombo General Hospital, with subacute effusive constrictive epicarditis. Three were male and two were female and the age range was from 16 to 46 years, four of the five being below 30 years. The clinical features of these patients are presented in the Table. Apart from the 16-year-old boy (case 1) who gave a history of one year's duration, the others had relatively short periods of illness varying from two to 12 weeks. In three of the patients (cases 2, 4, and 5) with short histories of two to six weeks, retrosternal or left-sided chest pain was a prominent symptom. All five patients complained of dyspnoea, and two were orthopnoeic. Four were febrile. The pulse volume was poor in all five patients but pulsus paradoxus (defined as an inspiratory fall in systolic arterial pressure greater than 10 mmHg) was not seen. The systolic blood pressure on admission was below 110 mmHg in four of the five patients. Jugular venous distension was present in four patients, only one (case 3) of whom had a positive Kussmaul's sign. A sharp y descent was present in two patients. The cardiac impulse was impalpable in four, and hepatomegaly, ankle oedema, and ascites were present in four patients, two patients, and one patient, respectively. A third heart sound was not heard in any of the five.

Pericardio-centesis	*ECG*	*Time interval from admission to operation*	*Operation*	*Aetiology*
0	Sinus rhythm, low voltage QRS, T ↓ in all leads	1 mth	PP normal, epi 2 mm, epicardiectomy only	Probably viral*
5 × (total 920 ml)	Sinus rhythm, low voltage QRS	2 wk	PP 10 mm, epi 7 mm, pericardiectomy	Tuberculosis
3 × (total 1950 ml)	Sinus rhythm, low voltage QRS, T ↓ in aVF and V6	2 d	PP 8 mm with calcification, epi 8 mm and infiltrating, pericardiectomy	Tuberculosis
2 × (total 400 ml)	Sinus rhythm, low voltage QRS	2 d	PP 4 mm, epi 10 mm, pericardiectomy	Pyogenic
2 × (total 550 ml)	Sinus rhythm, low voltage QRS	2 d	PP 4 mm, epi 3 mm, pericardiectomy	Probably viral*

Chest x-ray films showed conspicuous enlargement of the cardiac silhouette in all five (Fig. 1). In one (case 3), a small area of calcification was seen on the left lateral cardiac border. Low voltage QRS complexes were seen in all five electrocardiograms; all five patients were in sinus rhythm and P waves were normal. ST segment abnormalities were not seen, but minor T wave inversion was present in two patients.

The only patient with a long history (case 1) had another unusual feature: the enlargement of the heart was mainly to the right and the right border showed an angulation the significance of which was not certain (Fig. 2). He also had a firm enlarged cirrhotic liver with splenomegaly. Cardiac catheterisation showed a right atrial pressure of 12 mmHg and the right ventricular pressure record showed the typical early diastolic dip and raised end-diastolic pressure of constrictive pericarditis. Cineangiocardiography showed the heart to be displaced to the right with a small right ventricular cavity and a large pericardial effusion (Fig. 3). In view of these observations this patient was operated on without preceding aspiration.

In the remaining four patients the initial diagnosis was effusion with tamponade; two to five

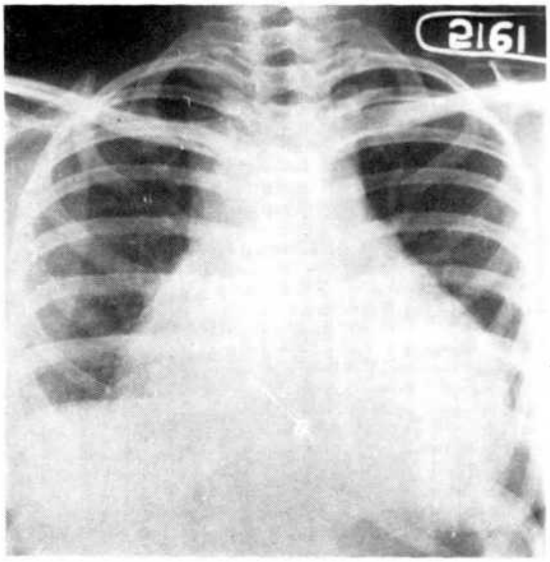

Fig. 1 *Chest* x-*ray film (case 5) showing enlarged cardiac shadow.*

aspirations were carried out in each of these patients. After each aspiration there was a slight increase in systolic blood pressure lasting only six to 12 hours. The raised venous pressure and hepatomegaly were unchanged. The aspirated fluid was thin in all and blood stained in three. The transient beneficial effect of pericardiocentesis and the overall deterioration was the indication for pericardiectomy, which was done two to 14 days after admission in these four patients.

At operation, the chest was opened through a median sternotomy incision in one while the other four had a left anterolateral thoracotomy. The pericardial effusion amounted to between 200 and 400 ml. The parietal pericardium was normal both macroscopically and histologically in one, slightly thickened in one, and grossly thickened in the remaining three patients. The epicardium varied from a taut white membrane no more than 2 mm thick to 8 mm thick in the two patients who were subsequently shown to have tuberculosis.

There were no adhesions between the two layers of pericardium. In all five there was considerable restriction of ventricular relaxation in diastole. Epicardiectomy alone sufficed in one, and in all five resulted in an obvious improvement in cardiac filling associated with a fall in the central venous pressure. In only case 3 was there any tendency for the epicardium to infiltrate the myocardium. The other four patients also required excision of the parietal pericardium. The immediate results were gratifying; three patients were discharged in excellent condition with normal blood pressure, normal venous pressure, and no oedema, hepatomegaly, or ascites. Two were much improved and when reviewed two years later showed further improvement, with no restriction of activity; residual hepatosplenomegaly in case 1 was attributed to cirrhosis. The histological appearance was that of tuberculosis in two and of acute pyogenic infection in one, and was consistent with a viral infection in the other two patients.

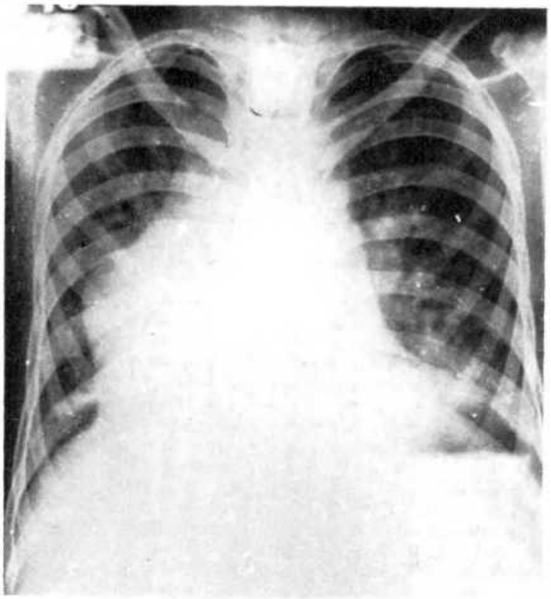

Fig. 2 *Chest x-ray film (case 1) showing displacement of cardiac shadow to the right with angulation of the right border.*

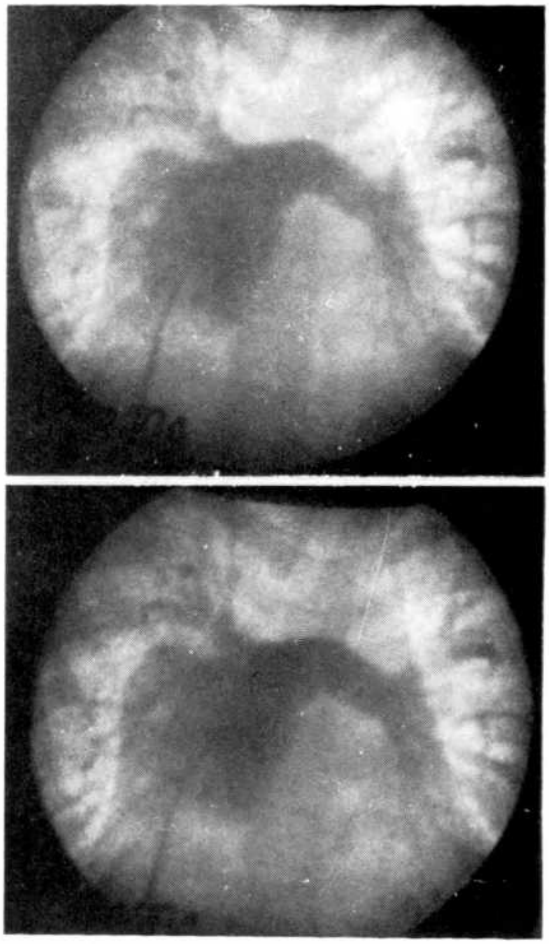

Fig. 3 *Right ventriculogram showing small ventricular cavity and large pericardial effusion (case 1).*

Discussion

Constriction is regarded as the culmination of chronic pericardial disease and has in the past been usually associated with tuberculosis.[4] Sporadic reports have appeared of patients proceeding to constriction after an illness as brief as two weeks, with symphysis of the two layers of pericardium.[14-16] Though the association of pericardial effusion and concomitant constrictive epicarditis has been infrequently reported, a review of the published cases shows that it occurs in many different diseases. The presenting clinical features with the exception of ascites may easily be confused with those of pericardial effusion with tamponade. Pulsus paradoxus was not observed by us though it has been described as being a feature of effusive constrictive disease.[17]

Hancock[13] analysed the clinical and haemodynamic features of effusive constrictive pericarditis, which were identical to those in our five cases, and drew attention to those features that were of diagnostic significance in distinguishing this condition from chronic constrictive pericarditis without effusion and pericardial effusion with tamponade. In his series pulsus paradoxus was more prominent in both effusive constrictive disease and effusion with tamponade than in chronic constriction without effusion. The characteristic third heart sound that is present in chronic constriction without effusion was rarely heard in the other two conditions, though similar sounds could be recorded on phonocardiograms in effusive constrictive disease, the presumption being that the sound was muffled by the fluid. Low voltage QRS complexes and flattened or inverted T waves were present in the electrocardiograms of both effusive constrictive disease and chronic constriction without effusion, but abnormal P waves were rare in the former. Kussmaul's sign was present in the jugular venous pulse, but pressure tracings indicated that, while in chronic constriction without effusion there was always a rise in right atrial pressure, in effusive constrictive disease there was an increase in the amplitude of the pulsations not always associated with a rise in right atrial mean pressure. The characteristic y descent of chronic constriction without effusion was not seen in effusive constrictive disease where either a more prominent systolic (x) descent was present or x and y descents were equal. However, in the effusive constrictive group the y descent became more obvious after pericardial aspiration. In four of our patients there was visible elevation of the venous pressure, and in the other (case 1) the right atrial mean pressure was high though the venous pressure was not seen to be raised. In only two of our cases was the y descent seen; an x descent was not seen in any case. No third heart sound was heard.

Hancock advocated simultaneous cardiac catheterisation and pericardiocentesis for the diagnosis of combined effusion and constriction. The diagnosis though not easily made initially should be strongly suspected from the poor response to pericardial aspiration and this should lead to pericardiectomy as the next step in treatment.

The constricting layer of epicardium may be deceptively thin and normal in appearance,[12] but the small heart size and restricted range of movement should indicate the presence of constriction. The parietal pericardium may be normal, in which case it should be left alone; however, if it is diseased, then excision of both visceral and parietal layers is necessary. Because of the dominant role of the epicardium in this disorder, the term epicarditis as first used by Burchell[2] and Edwards[3] is preferred to pericarditis. The constrictive epicardium in subacute effusive constrictive epicarditis shows a lesser tendency to infiltrate myocardium than in chronic constriction without effusion, though in both conditions piecemeal removal is usually necessary. The natural history appears to be progression to chronic constriction without effusion[13] and if left alone these cases will show the same tendency to myocardial infiltration as is seen in constriction without effusion.[6] It therefore seems expedient to carry out early pericardiectomy before the development of myocardial infiltration, which further compromises cardiac function and makes operation difficult. The good results obtained in this series confirm this view.

References

[1] Shabetai R, Fowler NO, Guntheroth WG. The hemodynamics of cardiac tamponade and constrictive pericarditis. *Am J Cardiol* 1970; **26:** 480–9.

[2] Burchell HB. Problems in the recognition and treatment of pericarditis. *J Lancet* 1954; **74:** 465–70.

[3] Edwards JE. *An atlas of acquired diseases of the heart and great vessels.* vol 1. London and Philadelphia: WB Saunders, 1961: 436–41.

[4] Wood P. Chronic constrictive pericarditis. *Am J Cardiol* 1961; **7:** 48–61.

[5] Spaulding JB. Subacute constrictive uremic pericarditis. *Arch Intern Med* 1967; **119:** 644–7.

[6] Mullen DC, Dillon ML, Young WG Jr, Sealy WC. Pericardiectomy in nontuberculous pericarditis. *J Thorac Cardiovasc Surg* 1969; **58:** 517–29.

[7] Steinberg I. Effusive constrictive radiation pericarditis. Two cases illustrating value of angiography in diagnosis. *Am J Cardiol* 1967; **19:** 434–9.

[8] Spodick DH, Kumar S. Subacute constrictive pericarditis with cardiac tamponade. *Dis Chest* 1968; **54:** 62–6.

[9] Rubinstein JJ, Goldblatt A, Daggett WM. Acute constriction complicating purulent pericarditis in

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Comparative echocardiographic features of conditions presenting with symptomatic pulmonary hypertension and right ventricular hypertrophy in early infancy*

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SUMMARY Echocardiographic dimensions in infants (less than 2 months) with pulmonary hypertension, associated with coarctation of the aorta in 21, total anomalous venous return in 10, and left-to-right shunts in 14 were compared with 10 infants with respiratory distress syndrome, seven with transient tachypnoea of the newborn, 20 normal children, and with each other. Distinguishing features of total anomalous pulmonary venous return were very significantly lower left atrial and left ventricular dimensions. Right ventricular enlargement was maximal in patients with coarctation of the aorta and total anomalous pulmonary venous return. Left ventricular end-diastolic dimension in coarctation of the aorta was not significantly different from normal but the left ventricular end-systolic dimension was significantly lower, suggesting a hypercontractile left ventricle. Similar findings were observed in patients with left-to-right shunts.

M-mode echocardiograms are hence valuable in differentiating conditions which may present with intractable congestive cardiac failure in the newborn and also distinguishing them from common respiratory disease of the neonate.

Congestive cardiac failure in the neonatal period is often associated with pulmonary hypertension. Several conditions such as coarctation of the aorta, large left-to-right shunts via ventricular septal defect, persistent ductus arteriosus, and atrial septal defect may occur singly or in combination. Total anomalous pulmonary venous return, usually with obstruction to the pulmonary veins, can present with intractable congestive cardiac failure. It is this latter condition that may be confused with respiratory distress syndrome since the radiological features often consist of an obscured cardiac shadow.[1]

Since the management of respiratory distress syndrome consists of continuous positive airway ventilation in addition to correction of acidosis, it is imperative that a precise diagnosis is made to avoid potentially hazardous cardiac investigations.

It is not uncommon to observe that the femoral arterial pulses vary in neonates with coarctation of the aorta.[2] Hence, it may not be possible to distinguish from other lesions causing congestive cardiac failure.

Echocardiographic features of coarctation of the aorta have been described recently.[3] Echocardiographic features of total anomalous pulmonary venous return were described,[4] though the implications of demonstrating an echo-free space behind the left atrium have been challenged.[5 6] The systolic time intervals, in the prognosis of neonates with respiratory distress syndrome, have been studied.[7] However, a comparative analysis of these conditions has not been made and superficial similarities consisting of an enlarged right ventricle may exist.

The purpose of this paper was to make a comparative analysis of the echocardiographic features of conditions presenting with pulmonary hypertension and congestive cardiac failure in the neonate. We believe that there are differentiating echocardiographic features that enable the clinician to make a more precise diagnosis.

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Subjects and methods

This study was performed on infants less than 2 months old admitted to The Hospital for Sick Children, Toronto, in congestive cardiac failure. The distribution of age and weight at the time of the study is set out in Table 1.

Initial assessment consisted of physical examination, chest radiograph, electrocardiogram, and M-mode echocardiogram. Twenty-one patients were diagnosed as having coarctation of the aorta (group 1). Ten with total anomalous pulmonary venous return formed group 2. Ten had respiratory distress syndrome and these with seven newborns with transient tachypnoea jointly formed group 3. Fourteen with large left-to-right shunts (Qp/Qs > 3:1) either had ventricular septal defect alone, in five, or in combination with persistent ductus arteriosus and atrial shunt, in nine, and jointly formed group 4. Finally, 20 patients without any cardiac or respiratory disease formed group 5, and served as controls.

The patients with coarctation of the aorta, total anomalous pulmonary venous return, and left-to-right shunts all underwent cardiac catheterisation and selective angiocardiography. All the patients in groups 1, 2, and 4 were found to have severe pulmonary hypertension at cardiac catheterisation: pulmonary artery pressure greater than 3/4 mmHg systemic. The patients with coarctation of the aorta did not have any associated intracardiac lesions apart from a small ventricular septal defect in nine (Qp/Qs < 1·5:1) and mild aortic stenosis in four (aortic valve gradient < 25 mmHg). Patients with total anomalous pulmonary venous return did not have any associated intracardiac lesions. Pulmonary venous return was to the innominate vein in five, superior vena cava in one, and infradiaphragmatic in three. The connection was mixed supracardiac in one.

Echocardiograms were obtained using a 5 MHz transducer (6 mm active diameter, non-focused) and Hoffrel 101C ultrasonic interfaced to a Cambridge recorder. Infants were examined at rest lying comfortably and without sedation. Recordings were obtained as described previously.[8] Systolic time intervals were measured from aortic and pulmonary valve leaflet motion recorded at 100 mm/s.[9] Echocardiograms were reviewed by at least two of the authors independently. The aortic root dimensions (Ao) were measured from the anterior margin of the posterior wall to the anterior margin of the

Table 1 *Age, weight distribution, right ventricular, left atrial, and aortic root dimension*

		Age (d)	*Weight (kg)*	*RVW (mm)*	*RVED (mm)*	*LAD (mm)*	*Ao (mm)*	*LA/Ao*
Group 1: Coarctation of aorta								
n=10	Living	18·1 (2–42)	3·46 (2·1–4·3)	3·6 ±1·8	15·1 ±5	16·3 ±2·8	9·4 ±1·9	1·74 ±0·4
n=11	Dying	8·8 (1–21)	3·52 (2·77–4·16)	4·4 ±0·7	17·4 ±4·6	14·9 ±3·3	9·0 ±1·3	1·69 ±0·8
n=21	Summary	13·2 (1–42)	3·49 (2·1–4·3)	3·95 ±1·28	17·2 ±4·8	15·6 ±3·1	9·2 ±1·6	1·72 ±0·6
Group 2: Total anomalous pulmonary venous return								
n=5	Living	19·8 (4–47)	2·94 (2·1–3·9)	4·2 ±0·8	15·8 ±5·2	10·4 ±1·6	8·4 ±1·8	1·24 ±0·2
n=5	Dying	22·0 (1–43)	3·29 (1·3–5·7)	3·4 ±1·5	15·4 ±3·4	8·6 ±2 7	7·0 ±1·0	1·2 ±0·2
n=10	Summary	20·9 (1–47)	3·42 (1·4–5·7)	3·8 ±1·15	15·6 ±4 3	9·5 ±2·15	7·7 ±1·4	1·22 (1·0–1·4)
Group 3: Transient tachypnoea of newborn								
n=7		1·37 (1–3)	3·2 (2 3–3 9)	3·4 ±0·7	8·3 ±3·9	13·1 ±2·6	8·8 ±0·5	1·49 ±0·6
	Respiratory distress syndrome							
n=10		4·5 (1–2·3)	3·6 (1·5–4·1)	3·0 ±0·6	10·8 ±3·1	11·9 ±2·1	8·9 ±0·9	1·33 ±0·42
Group 4: Left-to-right shunts (ventricular septal defects, persistent ductus arteriosus, atrial septal defect)								
n=14		24·6 (4–40)	2·54 (1·6–2·96)	3·2 ±0·8	12·5 ±3·43	15·8 ±3·72	9·3 ±1·14	1·64 ±0·4
Group 5: Normal								
n=20		9·2 (1–20)	3·2 (2·1–4·4)	2·5 ±0·45	10·0 ±0·95	13·0 ±1·35	10·0 ±0·75	1·3 ±0·5

RVW, right ventricular wall thickness; RVED, right ventricular end-diastolic diameter; LAD, left atrial diameter; Ao, aortic root diameter anterior wall at end-diastole.[10] Right ventricular wall thickness (RVW) was measured at end-diastole (onset of R wave) as was the right ventricular dimension (RVED). The right ventricular dimension was measured from the right septal surface to the epicardium.[11] Left ventricular dimensions were measured at end-systole (LVES), and end-diastole (LVED). Ejection fraction (EF) was determined from the left ventricular dimensions using a regression equation as suggested for infants.[12]

The ratio of pre-ejection period to ejection time was used to avoid the problem of variation of each individual index with heart rate.[9] [13]

The data was subjected to the Student's test for statistical significance. Mean echocardiographic measurements were compared by one-tailed or two-tailed t tests as appropriate. For instance, since we predicted that the left heart measurements in coarctation of the aorta (group 1) and left-to-right shunts (group 4) would be larger than those in total anomalous pulmonary venous return (group 2) one-tailed tests were used. When measurements were heteroscedastic, so that the usual t test could not be used, a variant due to Cochran was used.[14]

Results

The results have been set out in Tables 1 and 2.

GROUP 1: COARCTATION OF AORTA (NO. 21)
Right ventricular wall thickness and right ventricular end-diastolic dimensions were increased as compared with group 5 ($p < 0{\cdot}005$). Aortic root dimension and left ventricular end-diastolic dimension were slightly lower than normal ($p < 0{\cdot}05$ and $< 0{\cdot}03$). The left ventricular dimension at end-systole was, however, not significantly different. The left atrial to aortic root (LA/Ao) was increased.

There was no significant difference in the dimensions of the right and left ventricles between the patients with additional ventricular septal defects (nine patients) and those with isolated coarctation of the aorta. The left-to-right shunt through the ventricular septal defect, however, was small (P/S = 1·5/1). In another group of eight patients with large ventricular septal defects and a pulmonary/systemic ratio varying from 2/1 to 4/1 the right ventricular dimensions (RVED, RVES) and left ventricular end-diastolic dimensions

Table 2 *Left ventricular dimensions, ejection fraction, and systolic time intervals*

		Age *(d)*	*Weight* *(kg)*	*LVED* *(mm)*	*LVES* *(mm)*	*EF* (%)	*LSTI* *PEP/ET*	*RSTI* *PEP/ET*
Group 1: Coarctation of aorta								
n=10	Living	18·1	3·46	16·9	11·3	59·3	0·35	0·36
		(2–42)	(2·1–4·3)	±3·8	±2·1	±17·9	±0·24	±0·22
n=11	Dying	8·8	3·52	16·2	12·2	52·1	0·38	0·32
		(1–21)	(2·77–4·16)	±3·4	±0·7	±20·4	±0·28	±0·18
n=21	Summary	13·2	3·49	16·5	11·8	55·5	0·36	0·34
		(1–42)	(2·1–4·3)	±3·6	±1·4	±19·5	±0·26	±0·2
Group 2: Total anomalous pulmonary venous return								
n=5	Living	19·8	2·94	12·0	7·8	61·0	0·37	0·29
		(4–47)	(2·1–3·9)	±2·7	±1·4	±18·5	±0·22	±0·3
n=5	Dying	22·0	3·29	11·6	7·6	60·4	0·4	0·48
		(1–43)	(1·3–5·7)	±3·55	±0·9	±20·6	±0·22	±0·34
n=10	Summary	20·9	3·4	11·5	7·7	60·7	0·38	0·37
		(1–47)	(1·0–5·7)	±3·15	±1·15	±18·3	±0·22	±0·36
Group 3: Transient tachypnoea of newborn								
n=7		1·37	3·2	15·6	9·8	63·7	0·38	0·28
		(1–3)	(2·3–3·9)	±1·8	±2·2	±19·8	±0·12	±0·14
	Respiratory distress syndrome							
n=10		4·5	3·6	16·1	10·1	64·4	0·37	0·35
		(1–23)	(1·5–4·1)	±2·35	±1·65	±16·9	±0·26	±0·22
Group 4: Left-to-right shunts (ventricular septal defects, persistent ductus arteriosus, atrial septal defect)								
n=14		24·6	2·54	17·1	10·8	65·4	0·29	0·36
		(4–40)	(1·6–2·96)	±3·08	±2·01	±10·8	±0·12	±0·16
Group 5: Normal								
n=20		9·2	3·2	18·7	13·3	53·1	0·35	0·24
		(1–20)	(2·1–4·4)	±4·24	±1·6	±4·2	±0·06	±0·07

LVED, left ventricular end-diastolic diameter; LVES, left ventricular end-systolic diameter; EF, ejection fraction; LSTI, left-sided systolic time intervals; RSTI, right-sided systolic time intervals.

(LVED) were larger when compared with group 1 ($p < 0{\cdot}1$).

GROUP 2: TOTAL ANOMALOUS PULMONARY VENOUS RETURN (NO. 10)
Right ventricular wall thickness and right ventricular end-diastolic dimensions were increased ($p < 0{\cdot}005$). The left atrial and left ventricular dimensions were significantly less than normal ($p < 0{\cdot}001$). The LA/Ao ratio, however, was normal. The ventricular septal motion was normal in five, flat in three, and reversed in two.

GROUP 3: RESPIRATORY DISTRESS SYNDROME AND TRANSIENT TACHYPNOEA OF NEWBORN (NO. 17)
The echocardiographic dimensions did not differ significantly from normal apart from slightly lower left ventricular and aortic dimensions. This may be the result of the relatively younger age group (Tables 1 and 2).

GROUP 4: LEFT-TO-RIGHT SHUNTS (VENTRICULAR SEPTAL DEFECT AND VENTRICULAR SEPTAL DEFECT PLUS PERSISTENT DUCTUS ARTERIOSUS) (NO. 14)
The right ventricular wall thickness and right ventricular end-diastolic dimensions were only slightly increased as compared with normal ($p < 0{\cdot}01$ and $< 0{\cdot}025$). Neither the aortic root dimensions nor the left ventricular end-diastolic dimensions were significantly different. However, the left ventricular end-systolic dimension was significantly decreased ($p < 0{\cdot}001$). This finding confirmed the angiographic impression of a hypercontractile left ventricle in this group of patients.

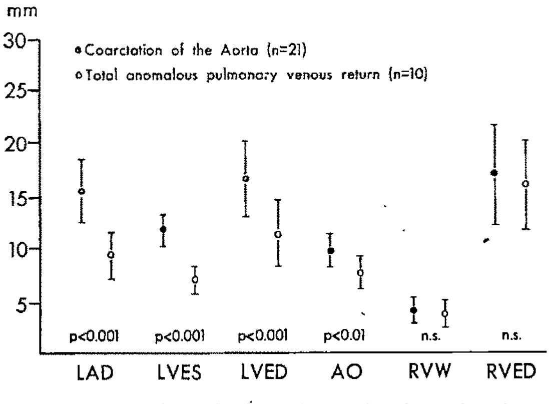

Fig. 1 *Comparison of echocardiographic dimensions in coarctation of the aorta (group 1) and total anomalous pulmonary venous return (group 2). p values are given for each value. Abbreviations as in Tables 1 and 2.*

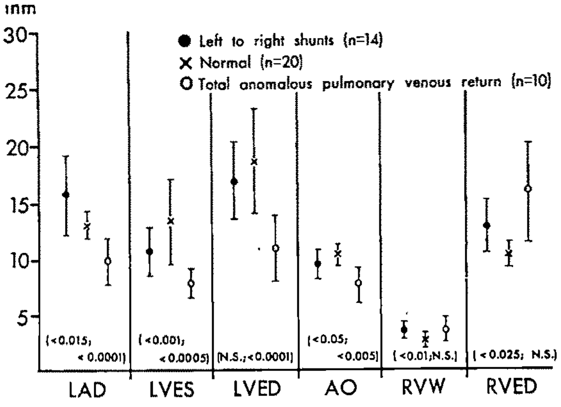

Fig. 2 *Comparison of echocardiographic dimension in left-to-right shunts (group 4), normal (group 5), and total anomalous pulmonary venous return (group 2). The p values in each column refer to comparison between group 4 versus group 5, and group 4 versus group 2.*

Therefore, patients in groups 1, 2, and 4 had increased right ventricular end-diastolic dimension and right ventricular wall thickness. Groups 1 and 4 had increased left atrial dimension, while group 2 had significantly low left atrial dimension and left ventricular end-diastolic dimension.

When echocardiographic dimensions of groups 1 and 2 were compared with each other (Fig. 1) left ventricular end-diastolic, end-systolic, and left atrial dimensions were significantly lower in patients with total anomalous pulmonary venous return ($p < 0{\cdot}001$). The aortic root dimension was also lower ($p < 0{\cdot}01$). When group 2 was compared with group 3, the most significant differences were lower left ventricular end-systolic, end-diastolic, left atrial, and aortic dimensions, and increased right ventricular wall and right ventricular end-diastolic dimension in group 2 (Tables 1 and 2). Similarly, when group 2 was compared with group 4, the most significant findings were lower left atrial, aortic, and left ventricular end-diastolic and end-systolic dimensions. Though the right ventricular wall and right ventricular end-diastolic dimensions were increased in group 2 as compared with group 4, the differences were not statistically significant (Fig. 2). Group 1 differed from group 4 in that the right ventricular wall and right ventricular end-diastolic dimensions were significantly thicker and larger. The systolic time intervals for the rigth ventricle in patients with total anomalous pulmonary venous return who died were increased compared with those who survived. The aortic root dimension was also reduced in those who died. However, in patients with coarctation of the aorta (group 1) no significant differences of ventricular function were observed in survivors compared with those who died (Table 2). Similarly, the contractility indices in groups 3 and 4 were not significantly different. Ventricular performance based on ejection fraction and systolic time intervals was also not significantly different among the various groups.

Discussion

Symptomatic coarctation of the aorta, total anomalous pulmonary venous return, and left-to-right shunting at ventricular and/or duct level all present with pulmonary hypertension as a major haemodynamic abnormality in early infancy. Superficial similarities exist between these. In addition, respiratory distress syndrome and transient tachypnoea of the newborn may be confused clinically. A full evaluation of the echocardiogram helps in the differential diagnosis.

Echocardiographic features of total anomalous pulmonary venous return have been described previously and include the demonstration of an echo-free space posterior to the left atrium.[4] However, this finding has also been observed in patients without total anomalous pulmonary venous return by us and others.[5 15] It may represent structures such as the coronary sinus and epicardial fat. It is therefore unreliable as the sole diagnostic feature. Septal motion in patients with total anomalous pulmonary venous return may either be normal, flat, or reversed. In our series, there was reversed motion in two, flat in three, and normal in five. There was no correlation between the septal motion and the left-to-right shunt or the presence of pulmonary venous obstruction. A previous study had suggested that the lack of paradoxical septal motion may be a result of the reduction of the left-to-right shunt in the presence of pulmonary venous obstruction.[16] The ejection fraction may be unreliable in the presence of abnormal septal motion. The right ventricular systolic time intervals were significantly prolonged in those who died. This has prognostic value in the clinical setting.

The significant differences between neonates with total anomalous pulmonary venous return (group 2) as compared with respiratory distress syndrome (group 3) consisted of lower left heart dimensions in group 2 (Tables 1 and 2). It is important that distinction between these two groups is made so that unnecessary and hazardous cardiac catheterisations in neonates with respiratory distress syndrome are avoided. By contrast, patients in group 2 require urgent cardiac catheterisations so that there is no deterioration before emergency surgery for reimplantation of the pulmonary venous trunk into the left atrium.

We believe that while there are no specific M-mode echocardiographic features of coarctation of the aorta and total anomalous pulmonary venous return, the echocardiographic dimensions of the left heart chambers usually help to differentiate the two groups (Fig. 1). Similarly, the group with left-to-right shunt caused by ventricular septal defect and persistent ductus arteriosus can also easily be distinguished from total anomalous pulmonary venous return on the basis of significantly increased left heart dimensions (Fig. 2). The left heart dimensions in groups 1 and 4 were not significantly different from each other but the right ventricular end-diastolic dimension and right ventricular wall thickness were significantly greater in group 1 ($p < 0{\cdot}002$ and $< 0{\cdot}05$, respectively).

Both coarctation of the aorta and total anomalous pulmonary venous return have enlarged right ventricular dimensions with thickened right ventricular wall. However, the left atrial, left ventricular, and aortic root dimensions are significantly lower in total anomalous pulmonary venous return. Angiocardiographic volume determinations in total anomalous pulmonary venous return have shown that the left atrial volume is reduced but the left ventricular volume is normal.[17] Similarly, an analysis of the geometry of the left ventricle in 36 fatal cases with total anomalous pulmonary venous return has shown that the left ventricular mass is within normal limits.[18] Hence, the lower left ventricle is pushed back and flattened by the enlarged right ventricle. Thus, though the minor dimension may be lower, the volume may not necessarily be reduced.

In our experience, the left heart dimensions in obstructed infradiaphragmatic total pulmonary venous return have always been smaller than normal. In such cases real-time echocardiographic examination using a xiphisternal approach may indeed show the absence of pulmonary veins entering the left atrium and also show the descending pulmonary venous trunk behind the left atrium.

Infants with coarctation of the aorta (group 1) and those with left-to-right shunts (group 4) were found to have normal left ventricular end-diastolic diameters but the left ventricular end-systolic dimensions were lower than in the normal group. This suggests a hypercontractile left ventricle as often seen on angiocardiography in these conditions.

Infants with total anomalous pulmonary venous return who died had a higher systolic time interval ratio (PEP/ET) as well as smaller aortic roots compared with those who survived. Echocardiographic features did not appear to have prognostic significance in the other groups.

Pulmonary hypertension is common to a number of cardiac anomalies in infancy. The causative haemodynamics are different in each condition. The M-mode echocardiogram tends to reflect these differences, and is of great help in arriving at a clinical diagnosis and also in planning the subsequent catheterisation and management of the patient.

References

1 Nadas AS, Fyler DC. *Pediatric cardiology*. 3rd ed. Philadelphia: WB Saunders, 1972: 645.
2 Rudolph AM. The changes in the circulation after birth. *Circulation* 1970; **41:** 343–59.
3 Wing AP, Findlay WA, Sahn DJ, McDonald G, Allen HD, Goldberg SJ. Serial echocardiographic profiles in infants and children with coarctation of the aorta. *Am J Cardiol* 1978; **41:** 1270–7.
4 Pacquet M, Gutgesel H. Echocardiographic features of total anomalous pulmonary venous connection. *Circulation* 1975; **51:** 599–605.
5 Bozio A, Davignon A. Interpreting the echocardiogram in TAPVC (letter to the editor). *Circulation* 1976; **53:** 1041–2.
6 Aziz KU, Paul MH, Bharati S, Lev M, Shannon K. Echocardiographic features of total anomalous pulmonary venous drainage into coronary sinus. *Am J Cardiol* 1978; **42:** 108–13.
7 Halliday H, Hirschfeld S, Riggs T, Liebman J, Fanaroff A, Bormuth C. Respiratory distress syndrome. Echocardiographic assessment of cardiovascular function and pulmonary vascular resistance. *Pediatrics* 1977; **60:** 444–9.
8 Bloom KR, Rodrigues L, Swan EM. Echocardiographic evaluation of left to right shunt in ventricular septal defect and persistent ductus arteriosus. *Br Heart J* 1977; **39:** 260–5.
9 Hirschfeld S, Meyer RA, Schwartz D, Korfhagen J, Kaplan S. Measurement of right and left systolic time intervals by echocardiography. *Circulation* 1975; **51:** 304–9.
10 Brown OR, Harrison DC, Popp RL. An improved method for echocardiographic detection of left atrial enlargement. *Circulation* 1974; **50:** 58–64.
11 Meyer RA. *Pediatric echocardiography*. Philadelphia: Lea & Febiger, 1977: 117.
12 Meyer RA, Stockert J, Kaplan S. Echocardiographic determinations of left ventricular volumes in pediatric patients. *Circulation* 1975; **51:** 297–303.
13 Riggs T, Hirschfeld S, Bormuth C, Fanaroff A, Liebman J. Neonatal circulatory changes: an echocardiographic study. *Pediatrics* 1977; **59:** 338–44.
14 Snedecor GW, Cochran WG. *Statistical methods*. 6th ed. Ames, Iowa: Iowa State University Press, 1967: 114–6.
15 Meyer RA. *Pediatric echocardiography*. Philadelphia: Lea & Febiger, 1977: 147.
16 Godman M, Tham P, Kidd BSL. Echocardiography in the evaluation of the cyanotic newborn infant. *Br Heart J* 1974; **36:** 154–66.
17 Graham TP Jr, Jarmakani JM, Canent RN Jr. Left heart volume characteristics with right ventricular volume overload. *Circulation* 1972; **45:** 389–96.
18 Bove KE, Geiser EA, Meyer RA. The left ventricle in total anomalous pulmonary venous return. Morphometric analysis of 36 cases fatal in infancy. *Arch Pathol* 1975; **99:** 522–8.

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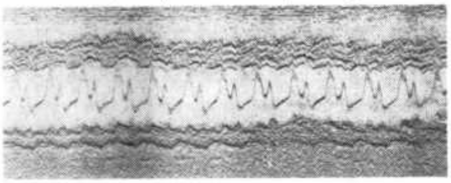

PHILIPS

Medical Systems

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These days, U.S. experts are taking care to recommend polyunsaturates.

1	**Inter-Society Commission for Heart Disease Resources 1970. "Primary prevention of atherosclerotic diseases."**	✓	**4**	**American Medical Association Council on Foods and Nutrition 1972. "Diet and Coronary Heart Disease."**	✓
2	**American Health Foundation 1972. "Diet and Coronary Heart Disease."**	✓	**5**	**Select Committee on Nutrition and Human Needs 1977. "Dietary goals for the United States."**	✓
3	**White House Conference 1973. "Nutrition policies in the Seventies."**	✓	**6**	**American Heart Association Committee on Nutrition 1978. "Diet and Coronary Heart Disease."**	✓

Six U.S. expert committees have now reported on diet and CHD.

All six recommend partial substitution of saturated fats by polyunsaturated fats.

The most recent report* advises that "the proportion of saturated fatty acids in the diet be brought into proper balance.

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"Polyunsaturated fatty acids should supply up to 10% of the total calories, which can be accomplished easily."

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*American Heart Association 1978. "Diet and coronary heart disease." General dietary recommendations – Section 2.

Br Heart J 1980; **44**: 55–61

Echocardiographic measurement of right ventricular wall thickness in adults by anterior approach

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SUMMARY The best way to record the right ventricular wall by echocardiography was investigated in 40 consecutive adult subjects with normal hearts and with various congenital and acquired cardiac disorders.

The right ventricular wall echo was recorded by (1) an anterior approach from the left sternal border in the supine position with 2·25 and 5·0 MHz transducers; (2) a subxiphoid approach with a 2·25 MHz transducer; and (3) an anterior approach in an 80-degree sitting position with 2·25 and 5·0 MHz transducers.

The highest successful recording rate (80%) was obtained by an anterior approach in the supine position with a 5·0 MHz transducer. The recording success rate by an anterior approach in the sitting position was 70 and 37·5 per cent with 5·0 and 2·25 MHz transducers, respectively, and the success rate by a subxiphoid approach was 50 per cent.

The normal range of the right ventricular wall thickness in 25 out of another 32 normal adults examined by the best way was 2·4±0·5 mm. When divided by body surface area, the normal right ventricular wall thickness index was 1·7±0·2 mm/m^2.

The right ventricular wall thickness of another 21 patients with right ventricular overload ranged from 2·5 to 16 mm, and seemed to correlate well with pulmonary arterial systolic pressure. The right ventricular wall thickness index had a better correlation with pulmonary arterial systolic pressure.

It is concluded that a 5·0 MHz transducer is more suitable for the recording of the right ventricular wall by a standard approach than a 2·25 MHz transducer, and this method would be useful for the diagnosis of right ventricular hypertrophy.

Echocardiography seems to have been widely used as a non-invasive method for the examination of the left side of the heart. For the right side there are many problems to be resolved. The method and its usefulness of recording the right ventricular wall by a subxiphoid approach have been previously reported,[1] but the usefulness of an anterior approach, especially in diagnosing right ventricular hypertrophy in adults, has not yet been established. For this reason the purpose of our present study was: (1) to find out the optimal method for recording the right ventricular wall; (2) to determine the normal range of the right ventricular wall thickness; and (3) to examine the usefulness for the diagnosis of right ventricular hypertrophy.

Subjects and methods

OPTIMAL METHOD OF RECORDING RIGHT VENTRICULAR WALL

The first object of the study was to find out the best method of recording the right ventricular wall. We studied 40 consecutive patients, 11 of whom were normal subjects, the remaining 29 having various cardiac disorders as shown in Table 1.

At first, each subject was examined echocardiographically in either the supine or left lateral decubitus position as a routine, after which we recorded the right ventricular wall.

The recordings of the right ventricular wall were done in five ways, namely, with 2·25 MHz and again with 5·0 MHz transducers parasternally at the third or fourth intercostal space, first in the supine or 15-degree left lateral decubitus position

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(anterior supine approach) (Fig. 1), and then with a 2·25 MHz transducer through the subxiphoid area (subxiphoid approach) (Fig. 2). Finally, the patients were raised passively to an approximate 80-degree sitting position and the recordings were taken with 2·25 and 5·0 MHz transducers from the left sternal border at the third or fourth intercostal space (anterior sitting approach) (Fig. 3).

For recording the right ventricular wall we chose the beam direction through which the maximal left ventricular transverse dimension could be recorded. When the right ventricular wall could not be recorded distinctly in this direction, the transducer was directed slightly towards the apex until the right ventricular wall endocardium became clear. We concluded each of our studies in one hour even if we were unsuccessful in obtaining a clear right ventricular recording.

The measurement of the right ventricular wall thickness was taken only at end-diastole, that is at the peak of the R wave on the electrocardiogram. We found that the quality of recording of the right ventricular wall was clear enough to estimate its thickness when the endocardium and epicardium were recorded distinctly at the end of diastole even if the endocardium of the right ventricular wall could not be recorded continuously throughout all of systole and diastole. After the tracings were obtained by our five recording methods, the percentage of those cases whose right ventricular wall thickness could be measured by each method was calculated.

Table 1 *Subjects used for study of transducer type and position*

Clinical diagnosis		*40 subjects*
Normal		11
Mitral valve disease	MS 6	9
	MR 3	
Aortic valve disease		2
Coronary artery disease	old MI 2	5
	angina 3	
Hypertension		2
Cardiomyopathy		2
Congenital heart disease	ASD 2	3
	VSD 1	
Others		6

ASD, atrial septal defect; old MI, old myocardial infarction; MR, mitral regurgitation; MS, mitral stenosis; VSD, ventricular septal defect.

NORMAL VALUE OF RIGHT VENTRICULAR WALL THICKNESS

In the second part of our study another 32 normal subjects, 28 men and four women with a mean age of 50·4 years (range 30 to 75), were studied to establish the normal range of right ventricular wall thickness.

These subjects visited our hospital for a check-up, and denied any cardiac symptoms. After the physical examination, chest *x*-ray, exercise electrocardiography (double Master's two-step test), and peripheral blood examinations these subjects were recorded as having no heart disease.

We recorded the right ventricular wall by the method which had the highest recording rate according to our findings, and on an enlarged scale so that we could measure the right ventricular wall

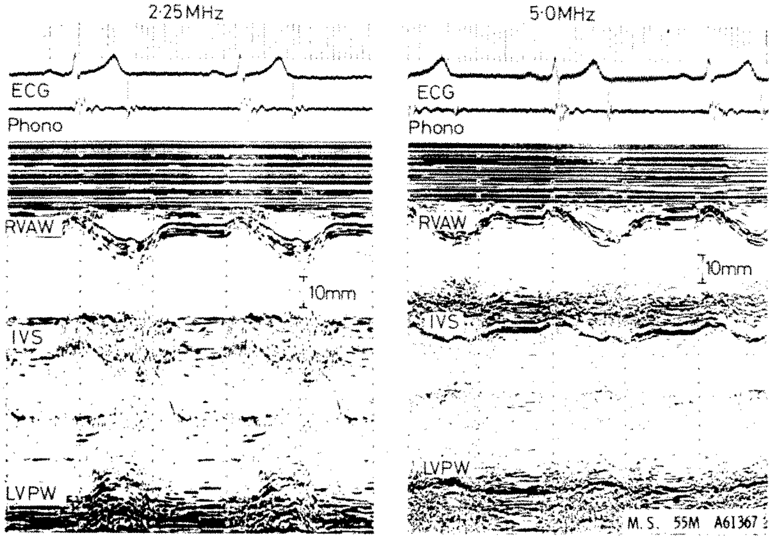

Fig. 1 *Tracings obtained by an anterior supine approach with 2·25 MHz* (left panel) *and 5·0 MHz* (right panel) *transducers. The scale between the right and left panels was different. Left ventricular posterior wall endocardium on the right panel was recorded poorly because ultrasound with higher frequency had greater absorption and scattering. IVS, interventricular septum; LV, left ventricle; LVPW, left ventricular posterior wall; RV, right ventricle; RVAW, right ventricular anterior wall.*

thickness accurately (Fig. 4). The thickness of the right ventricular wall was represented by the distance between the epicardial surface echo and the endocardial surface echo at the peak of the R wave on the electrocardiogram. The right ventricular thickness index was derived from dividing by the body surface area.

CORRELATION OF ECHOCARDIOGRAPHIC AND HAEMODYNAMIC FINDINGS

In the third part of our study, another 21 patients with various cardiac disorders of right ventricular overload as shown in Table 3, who underwent cardiac catheterisation, were studied to examine the feasibility of diagnosing right ventricular hypertrophy with echocardiography. The echocardiograms of the right ventricular anterior wall were recorded by the same method as the second part of the study. Correlation between the right ventricular anterior wall thickness and pulmonary arterial systolic pressure, and between the right ventricular anterior wall thickness index and pulmonary arterial systolic pressure, were studied.

The echocardiograms were obtained using an Irex echomodule interfaced Irex Continutrace 101 strip chart recorder. A 2·25 MHz, 12 mm diameter focused Irex ultrasound transducer and a 5·0 MHz, 6 mm diameter Irex or Aloka ultrasound transducer were used.

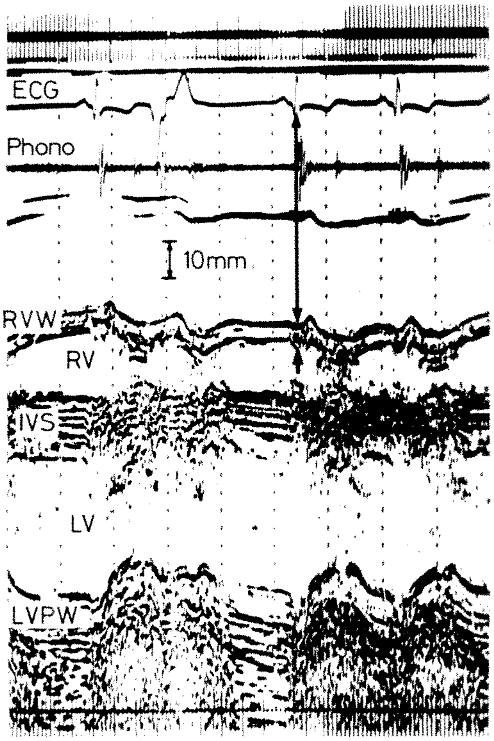

Fig. 2 *Tracings obtained by a subxiphoid approach with 2·25 MHz transducer. For abbreviations refer to Fig. 1.*

Results

OPTIMAL RECORDING

The tracings were obtained by the five recording

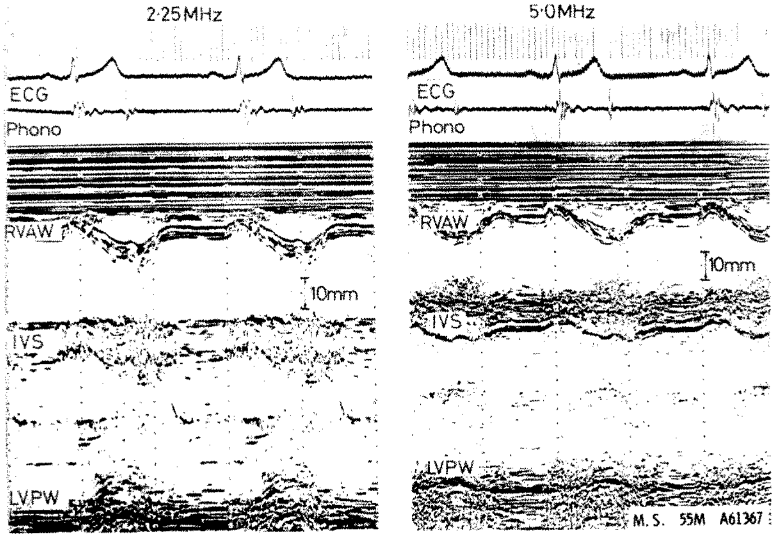

Fig. 3 *Tracings obtained by an anterior sitting approach with 2·25 MHz* (left panel) *and 5·0 MHz* (right panel) *transducers. For abbreviations refer to Fig. 1.*

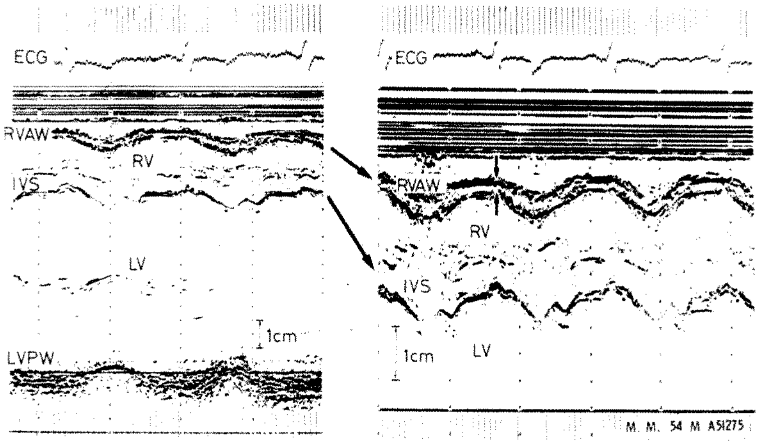

Fig. 4 *Right ventricular anterior wall recordings on an ordinary scale and an enlarged scale using an anterior supine approach with 5·0 MHz transducer. The right panel shows an expanded recording of the right ventricular anterior wall. The right ventricular wall thickness was measured from the upper border of the epicardial echo to the upper border of the endocardial echo. For abbreviations refer to Fig. 1.*

methods, and the percentage of cases whose right ventricular wall could be measured is shown in Table 2. Either in the supine or sitting position the rate of successful recording with the 5·0 MHz transducer was higher than with the 2·25 MHz transducer. The best method for recording was with the patient supine with a 5·0 MHz transducer (80%). Using a 2·25 MHz transducer in the supine position, the success rate was 47·5 per cent, and with the 2·25 and 5·0 MHz transducers in the sitting position it was 37·5 and 70 per cent, respectively. A subxiphoid approach with 2·25 MHz transducer gave a 50 per cent success rate. When a 5·0 MHz transducer was used in either the supine or sitting position, the success rate was 92·5 per cent.

NORMAL VALUE

By the best recording method of the right ventricular wall, that is the anterior approach in the supine position with a 5·0 MHz transducer, the righ ventricular walls were clearly recorded in 25 out o 32 normal subjects (78%). The normal thickness of the right ventricular anterior wall was 2·4 ± 0·5 mm (mean ±1 SD), ranging from 1·8 to 3·5 mm. The right ventricular anterior wall thickness index was 1·7 ± 0·2 mm/m² (mean ±1 SD).

Table 2 *Percentages of successful recordings of right ventricular wall by various methods (n = 40)*

Transducer	*Anterior approach*		*Subxiphoid approach*
	Supine	*Sitting*	
2·25 MHz	19 (47·5%)	15 (37·5%)	20 (50·0%)
5·0 MHz	32 (80·0%)	28 (70·0%)	

CORRELATION OF ECHOCARDIOGRAPHIC AND HAEMODYNAMIC FINDINGS

The right ventricular anterior wall thickness of the patients with right ventricular overload ranged from 2·5 to 16 mm (4·6 ± 3·1 mm (mean ±1SD)). The right ventricular anterior wall thickness index was between 1·6 and 10 mm/m² (3·3 ± 2·1 mm/m²). Pulmonary arterial systolic pressure ranged from 25 to 120 mmHg (53·8 ± 32·3 mmHg).

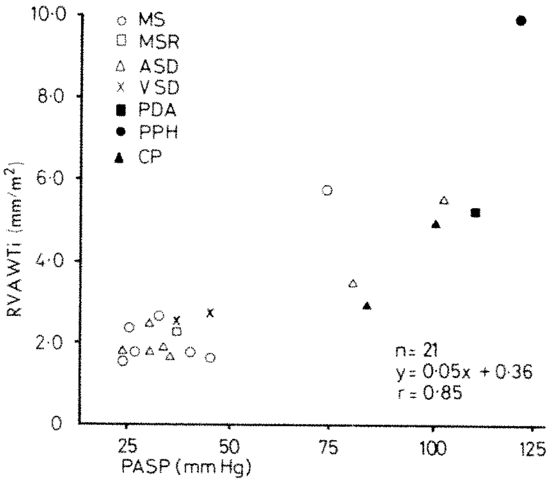

Fig. 5 *Relation between right ventricular anterior wall thickness index (RVAWTi) and pulmonary arterial systolic pressure (PASP). A good correlation was obtained (r = + 0·85). ASD, atrial septal defect; CP, cor pulmonale; MS, mitral stenosis; MSR, mitral stenosis with regurgitation; PDA, persistent ductus arteriosus; PPH, primary pulmonary hypertension; VSD, ventricular septal defect.*

The right ventricular anterior wall thickness had a good correlation with the pulmonary arterial systolic pressure (r = +0·77). The right ventricular anterior wall thickness index gave a better correlation with pulmonary arterial systolic pressure as shown in Fig. 5 (r = +0·85). An echocardiogram of the patient with primary pulmonary hypertension who had the thickest right ventricular anterior wall (16 mm) is shown in Fig. 6; his pulmonary arterial systolic pressure was 120 mmHg.

Discussion

There are many reports available concerning the measurement of the left ventricular wall thickness by echocardiography,[2–4] and its feasibility has been attested to by a good correlation with ventriculography,[5] and surgical inspection.[2] Reports related to the thickness of the right ventricular wall, however, have been limited to infants.[6–9] In adults it is only recently that the subxiphoid approach,[1] and the standard approach using a 2·25 MHz transducer[10 11] have been introduced. But the measurement of right ventricular anterior wall thickness by a standard approach with a 2·25 MHz transducer is usually uncertain because of poor recording.[12]

The impetus to perform this study first came to us when we encountered a patient who could not assume the supine position because of dyspnoea during an echocardiographic examination. We found that we could make a distinct record of the right ventricular anterior wall endocardium by an anterior approach, with the patient in the sitting position. Then we tried an anterior sitting approach as well as the anterior supine and subxiphoid approach.

Table 3 *Echocardiographic and haemodynamic data in 21 patients with right ventricular overload*

Case no.	*Age and sex*		*Diagnosis*	*BSA* (m^2)	*RVAWT* (*mm*)	*RVAWTi* (mm/m^2)	*PAP* (*mmHg*)
1	41	M	ASD	1·44	8·0	5·6	102/50
2	55	F	ASD	1·14	4·0	3·5	80/35
3	42	F	ASD	1·50	4·0	2·7	32/12
4	45	F	ASD	1·58	4·5	2·8	30/15
5	44	M	ASD	1·70	3·0	1·8	23/7
6	65	F	ASD	1·38	3·5	2·5	30/12
7	22	F	ASD	1·44	2·5	1·7	35/10
8	55	M	ASD	1·00	3·0	1·9	33/15
9	56	M	VSD	1·43	4·0	2·8	45/14
10	24	M	VSD	1·55	4·0	2·6	36/15
11	45	F	PDA	1·16	6·0	5·2	110/70
12	46	M	PPH	1·60	16·0	10·0	120/60
13	49	M	CP	1·40	7·0	5·0	100/55
14	56	F	CP	1·35	4·0	3·0	84/40
15	55	F	MSR	1·39	8·0	5·8	74/30
16	36	F	MS	1·26	3·0	2·4	25/14
17	56	F	MS	1·37	2·5	1·8	40/17
18	37	F	MS	1·40	2·5	1·8	26/10
19	53	F	MS	1·43	2·5	1·7	45/25
20	45	F	MS	1·52	2·5	1·6	23/8
21	45	F	MSR	1·31	3·0	2·3	36/16

ASD, atrial septal defect; BSA, body surface area; CP, cor pulmonale; MS, mitral stenosis; MSR, mitral stenosis with regurgitation; PAP, pulmonary artery pressure; PDA, persistent ductus arteriosus; PPH, primary pulmonary hypertension; RVAWT, right ventricular anterior wall thickness; RVAWTi, right ventricular anterior wall thickness index; VSD, ventricular septal defect.

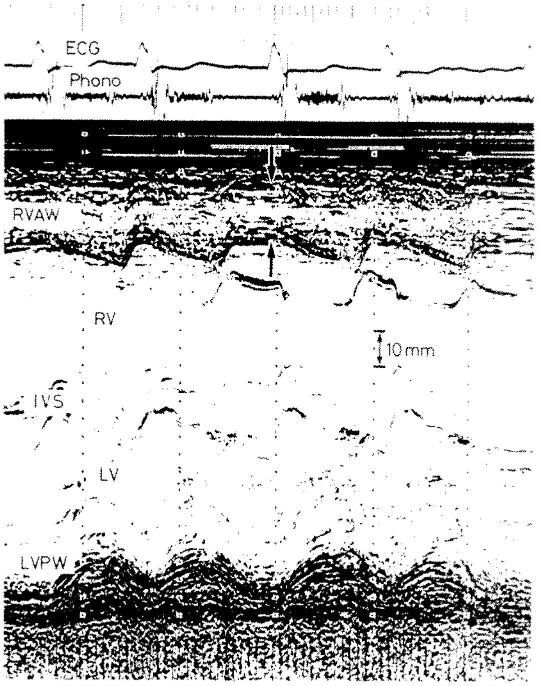

Fig. 6 *Echocardiogram by anterior approach with 5·0 MHz transducer in a 46-year-old man with primary pulmonary hypertension (case 12 in Table 3). The right ventricular anterior wall thickness is 16 mm, as indicated by arrows.*

BEST METHOD OF RECORDING RIGHT VENTRICULAR WALL

We found that an anterior supine approach with a 5·0 MHz transducer gave the best results. It is well known that the higher the frequency of a transducer, the greater its resolving power. Our results seem to bear this out. It has been reported that the success rate by a subxiphoid approach was 90·6 per cent[1] but in our study it was only 50 per cent. Since one of the requirements in the routine examination is to shorten its duration as much as possible, we have limited the time required for one case to 60 minutes. If we had taken longer than our limit of 60 minutes for each method, the percentage of successful recordings might have been slightly higher. However, in comparing the results obtained under the same conditions by our five methods, the recording success rate by an anterior supine approach was highest.

NORMAL VALUE

The normal value of the right ventricular wall thickness proved to be 2·4 ±0·5 mm, which seems to coincide well with the findings in hearts in Japan brought to necropsy. It has been said that the normal right ventricular wall thickness is from 2 to 3 mm, and right ventricular hypertrophy is diagnosed when right ventricular wall thickness is 3·5 mm or more in necropsied hearts.[13] By a subxiphoid approach the right ventricular wall thickness has been reported to have a normal range of 3·4 ±0·8 mm.[1] Though there are differences between anterior and subxiphoid approaches, our normal values have correlated with those of hearts coming to necropsy[13] when we used an anterior supine approach. Recording through the subxiphoid may give a slightly greater value because the ultrasonic beam may traverse the right ventricular wall diagonally.

To record the right ventricular wall we chose the beam direction through which the maximal left ventricular transverse dimension could be recorded. When the right ventricular wall could not be recorded distinctly in this direction, the transducer was directed slightly towards the apex until the right ventricular wall endocardium became clear. We believe that this beam direction would also be useful in measuring right ventricular wall thickness more accurately because the beam should traverse the right ventricular wall perpendicularly in order to record it distinctly.

VALIDITY OF ANTERIOR APPROACH WITH 5·0 MHZ TRANSDUCER

The right ventricular anterior wall thickness correlated well with pulmonary arterial systolic pressure. In all 21 patients with right ventricular overload, pulmonary arterial systolic pressure was equal to the peak systolic pressure of the right ventricle because there was no obstruction between the pulmonary artery and the right ventricle. We consider that the right ventricular anterior wall thickness increases in proportion as pulmonary arterial systolic pressure increases whether the right ventricle is volume-overloaded or pressure-overloaded.

The correlation coefficient between the right ventricular anterior wall thickness index and the pulmonary arterial systolic pressure was higher than that between the right ventricular anterior wall thickness and the pulmonary arterial systolic pressure. This indicates that the right ventricular anterior wall thickness index is more suitable for diagnosing right ventricular hypertrophy than the absolute value of the right ventricular anterior wall thickness.

CLINICAL IMPLICATION

Electrocardiographically, it is often difficult to diagnose right ventricular hypertrophy and biventricular hypertrophy, especially in cases with bundle-branch block or Wolff-Parkinson-White syndrome. Sometimes it is also difficult to differentiate right ventricular hypertrophy from true posterior wall infarction. The present study indicates that echocardiography by standard approach with a 5·0 MHz transducer is useful for diagnosing right ventricular hypertrophy even in these cases because this method provides an adequate visualisation of the right ventricular anterior wall, facilitating the measurement of its thickness.

Conclusion

(1) The best method of recording the right ventricular wall after testing two transducers and three approaches proved to be an anterior approach in the supine position with a 5·0 MHz transducer.

(2) The normal range of the right ventricular wall thickness measured in 25 normal subjects by the best recording method was 2·4 ±0·5 mm. This gave the thickness index of 1·7 ±0·2 when divided by body surface area.

(3) Recording the right ventricular wall can be made successfully by a standard approach (anterior approach) when a 5·0 MHz transducer is used, and this method is considered to be valuable in the diagnosis of right ventricular hypertrophy.

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References

1 Matsukubo H, Matsuura T, Endo N, *et al.* Echocardiographic measurement of right ventricular wall thickness: a new application of subxiphoid echocardiography. *Circulation* 1977; **56:** 278–84.
2 Feigenbaum H, Popp RL, Chip JN, Haine CL. Left ventricular wall thickness measured by ultrasound. *Arch Intern Med* 1968; **121:** 391–5.
3 Sjögren A-L, Hytönen I, Frick MH. Ultrasonic

measurement of ventricular wall thickness. *Chest* 1970; **57:** 37–40.

4 Askanas A, Rajszys R, Sadonski Z, Stopczyk M. Measurement of the thickness of the left ventricular wall in man using the ultrasound technique. *Pol Med J* 1970; **9:** 62–6.

5 Feigenbaum H, Popp RL, Wolfe SB, *et al.* Ultrasound measurements of the left ventricle. A correlative study with angiography. *Arch Intern Med* 1972; **129:** 461–7.

6 Solinger R, Elbl F, Minhas K. Echocardiography in the normal neonate. *Circulation* 1973; **47:** 108–18.

7 Hagan AD, Deely WJ, Sahn DJ, Fiedman WF. Echocardiographic criteria for normal newborn infants. *Circulation* 1973; **48:** 1221–6.

8 Goldberg SJ, Allen HD, Sahn DJ. *Pediatric and adolescent echocardiography.* Chicago: Year Book Medical Publishers, 1975: 35.

9 Gewitz M, Eshaghpour E, Holselaw DS, Miller HA, Kawai N. Echocardiography in cystic fibrosis. *Am J Dis Child* 1977; **131:** 275–80.

10 Prakash R, Lindsay P. Determination of right ventricular wall thickness by echocardiogram. *JAMA* 1978; **239:** 638–40.

11 Prakash R. Determination of right ventricular wall thickness in systole and diastole. Echocardiographic and necropsy correlation in 32 patients. *Br Heart J* 1978; **40:** 1257–61.

12 Sahn DJ, Denaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; **58:** 1072–83.

13 Mori S. *Textbook of special pathology* (in Japanese). Tokyo: Kanehara Publication, 1964, 22.

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Evidence for emotionally-induced coronary arterial spasm in patients with angina pectoris*

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SUMMARY Twelve executives with typical angina pectoris, given a 12-minute quiz, designed to be psychologically stressful, responded with ST depressions of $\geqslant 1{\cdot}0$ mm. Each of these patients was given an exercise tolerance test on an upright bicycle to induce an amount of ST depression equivalent to that observed during the quiz. A statistical analysis was made of the products of the heart rate and the systolic blood pressure (rate-pressure product), at the onset of equivalent ST depression on both tests. At the maximal ST depression during the quiz, the mean rate-pressure product was 181 ± 64 (SD) $\times 10^2$, and at an equivalent ST depression during exercise it was $225 \pm 54 \times 10^2$; the mean difference was $44 \pm 40 \times 10^2$.

Inasmuch as the rate-pressure product is an index of myocardial oxygen consumption, the differences in rate-pressure product suggest that myocardial ischaemia occurred at a lower myocardial oxygen consumption during emotional stress than during exercise. If equivalent degrees of ST depression during exercise and the quiz are indicative of equivalent ischaemia, then a relative reduction in coronary blood flow during emotional stress, probably by coronary spasm, may be postulated as the most reasonable explanation for these observations.

It has been observed that, in patients with angina pectoris, chest pain tends to be produced whenever the myocardial oxygen consumption exceeds a critical value.[1] Whether the angina occurred spontaneously or in response to exercise, it seemed always to recur at about the same myocardial oxygen consumption for each patient. These results furthered the theory that angina was produced by a fixed atherosclerotic coronary lesion and seemed to refute a role for coronary spasm in the syndrome of typical angina pectoris. Robinson[1] reported one patient who developed angina in response to performing mental arithmetic as well as to exercise. Using the rate-pressure product (heart rate multiplied by systolic blood pressure) as an index of myocardial oxygen consumption, he noted that the rate-pressure products were similar at the onset of the angina, regardless of how it was provoked. He suggested that emotional stress, like exercise, provokes angina by increasing the myocardial oxygen consumption above a critical level.

We examined the relation between angina pectoris and emotional stress using a larger patient population and electrocardiographic criteria for myocardial ischaemia, rather than subjective patient reporting. A comparison was made of the rate-pressure products at the time of equivalent ST responses to exercise and to emotional stress.

Subjects and methods

Thirty-six patients with angina pectoris and not taking digitalis were given a 12-minute tape recorded quiz, designed to be stressful, while the electrocardiogram and blood pressure were being monitored. A full description of the quiz electrocardiogram has been reported.[2] Those patients manifesting at least 1 mm of ST segment depression in response to the quiz were selected for exercise tolerance testing.

Each patient, upon arrival at the cardiovascular laboratory, was familiarised with the laboratory and

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then asked for written informed consent to the study. The tests were given without cost or remuneration to the patient. After a detailed history and physical examination, a 12 lead, supine, resting electrocardiogram was recorded. A brief unstructured psychiatric interview was also conducted. No patient was accepted for study who manifested unstable angina, recent myocardial infarction (within six weeks), unstable resting electrocardiogram, or other significant illness except stable hypertension. All tests were performed in an exercise laboratory, using the same precautions as are used for tolerance testing.[3] For both the quiz electrocardiogram and the exercise tolerance test, exercise electrocardiographic electrodes were applied as described by Mason and Likar.[4] The electrocardiogram was calibrated to 1 mV/10 mm, and the response signal was evaluated before each test. Blood pressure measurements were obtained by auscultation using a standard sphygmomanometer. Diastolic blood pressure was determined by the disappearance of the Korotkoff sounds.

A baseline electrocardiogram was recorded with the exercise electrodes, with the patient sitting in the same position used during exercise and the quiz. Three baseline blood pressure readings were also taken.

Subjects were then instructed to answer questions asked on a 12-minute tape recording.[2] During this quiz, the electrocardiogram was monitored continuously, and the blood pressure was measured at least every two minutes.

The 12 patients with positive responses to the quiz electrocardiogram constituted the study group. They were given an upright bicycle exercise tolerance test to induce an equivalent ST segment depression. Progressively more intense four-minute work loads, each followed by a five-minute rest period, were used. Blood pressure was measured by auscultation during the last minute of each exercise load, or at the onset of ST segment depression.

Most of the exercise tests were performed on the same day as the quiz electrocardiogram, with a 45-minute rest period between tests. When the tests were performed on different days, they were performed within 48 hours of each other. Both the quiz electrocardiogram and the exercise tolerance test used the same monitoring leads, and were conducted at a room temperature of 21°C (70°F) and at approximately the same time of day with patients in the fasting state and in the same body position.

Using the criteria of Ellestad and Wan,[5] the ST segments were carefully measured with a magnifying glass, using the PQ junction as a reference. The ST segment depression at 0·08 second after the J point was considered as the extent of depression. Each reported ST segment value represented the average of the measurements of 10 consecutive beats.

All the patients in this study were executives, defined as those whose occupation is classified by the US Bureau of the Census as either professional, managerial, or sales.[6] A previous study has shown that executives tend to respond significantly more to the quiz electrocardiogram than do non-executives.[2]

The study group consisted of 11 men and one woman, aged 52 to 69 years (mean 62). All had typical angina, defined as recurrent chest pressure discomfort of brief duration, usually precipitated by physical exertion. Two had undergone coronary angiography, each revealing at least 70 per cent occlusion of a coronary artery; five had a history of a documented myocardial infarction; and two had a history of hypertension. One patient was taking propranolol at the time of the study; otherwise no medication known to affect the cardiovascular system was taken for 72 hours before the study. The 12 patients in the study group did not differ from the 24 patients who had less than 1·0 mm ST depression on the questionnaire, with regard to physical examination, history, or psychiatric interview.

Results

ST SEGMENT RESPONSES

In each of the 12 patients who developed $\geqslant 1{\cdot}0$ mm ST segment depression during the quiz electrocardiogram, exercise testing was able to induce an amount of ST segment depression equivalent to that on the quiz. The Figure shows the equivalent ST segment changes for four patients. No patient developed chest pain during the study.

DIFFERENCES IN THE RATE-PRESSURE PRODUCTS

The Table presents the individual heart rates, blood pressures, and rate-pressure products for both tests at the onset of ST segment depression. A statistical analysis was made of the rate-pressure products at the time of equivalent ST segment depressions on both tests. At the time of maximal ST depression during the quiz, the mean rate-pressure product was 181 ± 64 (SD) $\times 10^2$, and at an equivalent ST depression during exercise it was 225 ± 54 (SD) $\times 10^2$. The mean difference was 44 ± 40 (SD) $\times 10^2$. By paired t test p was $<0{\cdot}005$.

Discussion

Roughgarden[7] reported that patients with spon-

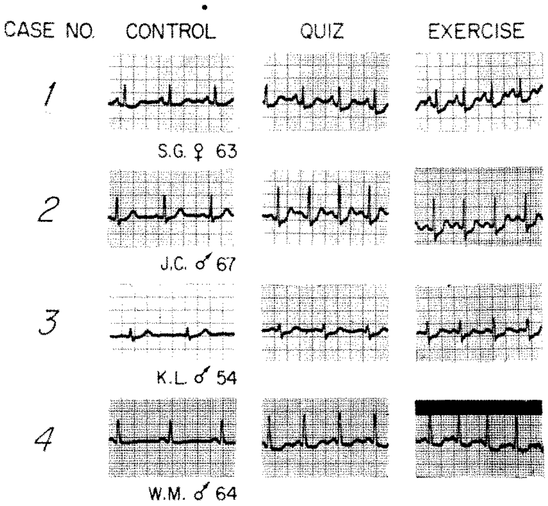

Fig. *The control electrocardiograms before the quiz and the equivalent electrocardiographic response to the quiz and to exercise of four patients with typical angina pectoris. None of these patients had undergone angiography, and none was taking drugs at the time of study. All tracings were recorded from lead V5 with the exception of those of case 1 which were recorded from lead II.*

taneous angina had symptoms that were preceded by increases in heart rate and blood pressure. Similarly, Robinson[1] showed that 15 patients with angina pectoris, who exercised on two or more occasions, had angina which tended to occur when a critical rate-pressure product was exceeded. He also reported one patient who developed angina in response to the emotional stress of performing mental arithmetic, as well as to an exercise stress. In that patient, angina occurred when a critical rate-pressure product was exceeded, regardless of the type of provocative stress. The work of Roughgarden[7] and Robinson[1] thus tends to argue against a significant role for coronary spasm in ischaemic heart disease.

Using the same basic arguments as Robinson,[1] we hypothesised that if ischaemia were the result of a fixed coronary blockage, then the myocardial oxygen consumption at the onset of ischaemia should be the same regardless of how the ischaemia was provoked. In 12 patients we were able to provoke ST segment responses suggesting ischaemia under two conditions: emotional stress and physical stress. Ischaemic ST responses occurred at significantly lower rate-pressure products during emotional stress than during exercise stress. If ST depression during exercise had occurred when a "critical" rate-pressure product was reached, then during the emotional stress the ST depression occurred at a point significantly below the alleged "critical" rate-pressure product.

The rate-pressure product is considered to be a valid index of myocardial oxygen consumption.[8–10] The occurrence of ST segment depression at a lower rate-pressure product reflects less coronary blood flow only if the myocardial oxygen demands are faithfully reflected in the rate-pressure product. Increased left ventricular volume leads to increased wall tension, and thus myocardial oxygen uptake is increased for any given rate-pressure product.[11] Hence, if ventricular volume were greater for the psychological stress than during exercise, more ST segment depression would be expected. In this

Table *Individual heart rates, blood pressures, and rate-pressure products at time of equivalent ST responses to quiz and to exercise*

Case no.	*Quiz electrocardiogram*				*Exercise electrocardiogram*			
	Heart rate (b/min)	*Systolic blood pressure (mmHg)*	*Diastolic blood pressure (mmHg)*	*Rate × pressure × 10²*	*Heart rate (b/min)*	*Systolic blood pressure (mmHg)*	*Diastolic blood pressure (mmHg)*	*Rate × pressure × 10²*
1	110	184	120	202	140	190	106	266
2	112	180	92	202	129	200	110	258
3	72	168	94	121	112	186	104	208
4	83	150	86	124	95	148	80	141
5	150	190	120	285	120	210	110	252
6	96	145	80	139	113	166	80	188
7	79	170	98	134	100	210	110	210
8	130	230	104	299	136	230	110	313
9	113	188	100	212	121	164	86	199
10	108	154	96	166	128	164	102	210
11	110	182	108	200	145	208	120	302
12	64	144	92	92	92	168	96	155
	**	*	NS	***				
Mean ± SD	102 ± 25	174 ± 24	99 ± 12	181 ± 64	119 ± 17	187 ± 25	101 ± 13	225 ± 54

* $p \leqslant 0{\cdot}02$ (compared with exercise); ** $p \leqslant 0{\cdot}01$ (compared with exercise); *** $p \leqslant 0{\cdot}005$ (compared with exercise);
NS, not significant; SD, standard deviation.

study, at the time of the equivalent ST depression, the systolic pressure was slightly but significantly lower during the emotional quiz compared to exercise. This lower pressure would be expected to be associated with a lesser ventricular volume. Also, during exercise, the increased venous return would be expected to lead to a larger ventricular volume than during emotional stress.[12 13] On the other hand, emotional stress may be associated with increased venous tone[14] which might lead to an increase in central venous pressure and ventricular volume. Therefore, alterations of ventricular volume have not been ruled out. Myocardial contractility may also affect myocardial oxygen demands[15] and, in view of the higher heart rate during exercise, may have been higher during exercise stress.

We compared the rate-pressure products at equivalent amounts of ST segment depression during the exercise and emotional stress. Though it cannot be considered proven that equivalent amounts of ST segment depression represent equivalent amounts of ischaemia, this assertion is supported by work in animals.[16 17] ST segment depression is a more objective index of the degree of myocardial ischaemia than subjective reporting of a chest discomfort.

If the rate-pressure product adequately reflects the myocardial oxygen consumption, and if equivalent amounts of ST segment depression represent equivalent amounts of ischaemia, then the most likely explanation for our findings is that emotional stress provoked a transient, relative decrease in myocardial oxygen delivery. A hypothesis that a shift in the oxyhaemoglobin curve could produce clinical ischaemia has not been sustained.[18] A hypothesis that platelet aggregation might cause a transient coronary obstruction has some support from work on a dog preparation,[19] but has not yet been demonstrated to have clinical significance in angina patients. Generalised or local constriction—or even local dilatation—of coronary resistance vessels are potential but unproven pathophysiological mechanisms by which emotion might induce ischaemia. Furthermore, ST and T changes resembling myocardial ischaemia have been encountered at rest in healthy men with normal coronary arteriograms and attributed to catecholamine hypersecretion or hypersensitivity.[20] On the other hand, it is known that the conducting coronary arteries contain smooth muscle which is sensitive to neural and chemical stimulation and which has been repeatedly shown by coronary visualisation to cause clinically significant coronary spasm.[21–23]

Our observations in patients with classical angina are compatible with the hypothesis that coronary artery spasm, in addition to atherosclerosis, may play a role in the production of the ischaemic electrocardiographic responses to emotional stress.

References

[1] Robinson BF. Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation* 1967; **35:** 1073–83.

[2] Schiffer F, Hartley LH, Schulman CL, Abelmann WH. The quiz electrocardiogram: a new diagnostic and research technique for evaluating the relation between emotional stress and ischemic heart disease. *Am J Cardiol* 1976; **37:** 41–7.

[3] Bruce RA, Irvine JB. Exercise electrocardiography. In: Hurst JW, ed. *The heart, arteries and veins.* New York: McGraw-Hill, 1978: 336.

[4] Mason RE, Likar I. A new system of multiple-lead exercise electrocardiography. *Am Heart J* 1966; **71:** 196–205.

[5] Ellestad MH, Wan KC. Predictive implications of stress testing: follow-up of 2700 subjects after maximum treadmill stress testing. *Circulation* 1975; **51:** 363–9.

[6] United States. Bureau of the Census. Occupation by Industry. Census of Population 1970. PC (2) —7C. Washington, DC: US Government Printing Office, 1973–4.

[7] Roughgarden JW. Circulatory changes associated with spontaneous angina pectoris. *Am J Med* 1966; **41:** 947–61.

[8] Sarnoff SJ, Braunwald E, Welch GH Jr, Case RB, Stainsby WN, Macruz R. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am J Physiol* 1958; **192:** 148–56.

[9] Kitamura K, Jorgensen CR, Gobel FL, Taylor HL, Wang Y. Hemodynamic correlates of myocardial oxygen consumption during upright exercise. *J Appl Physiol* 1972; **32:** 516–22.

[10] Gobel FL, Norstrom LA, Nelson RR, Jorgensen CR, Wang Y. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation* 1978; **57:** 549–56.

[11] Monroe RG, French GN. Left ventricular pressure-volume relationships and myocardial oxygen consumption in the isolated heart. *Circ Res* 1961; **9:** 362–74.

[12] Lichtlen P. The hemodynamics of clinical ischemic heart disease. *Ann Clin Res* 1971; **3:** 333–43.

[13] Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS. Real-time radionuclide cineangiography in the non-invasive evaluation of global and regional left ventricular function at rest and during exercise in patient with coronary artery disease. *N Engl J Med* 1977; **296:** 839–44.

[14] Duggan JJ, Love VL, Lyons RH. A study of reflex venomotor reactions in man. *Circulation* 1953; **7:** 869–75.

[15] Sonnenblick EH, Morrow AG, Williams JF Jr. Effects

of heart rate on the dynamics of force development in the intact human ventricle. *Circulation* 1966; **33:** 945–51.

[16]Ekmekci A, Toyoshima H, Kowczynski JK, Nagaya T, Prinzmetal M. Angina pectoris IV: clinical and experimental differences between ischemia with ST elevation and ischemia with ST depression. *Am J Cardiol* 1975; **51:** 363–9.

[17]Case RB, Roselle HA, Crangster RS. Relation of ST depression to metabolic and hemodynamic events. *Cardiologia* 1966; **48:** 32–41.

[18]Vokonas PS, Cohn PF, Klein MD, Laver MB, Gorlin R. Hemoglobin affinity for oxygen in the anginal syndrome with normal coronary arteriograms (abstract). *Am J Cardiol* 1970; **26:** 664–5.

[19]Folts JD, Crowell EB Jr, Rowe GG. Platelet aggregation in partially obstructed vessels and its elimination with aspirin. *Circulation* 1976; **54:** 365–70.

[20]Taggart P, Carruthers M, Joseph S, *et al.* Electrocardiographic changes resembling myocardial ischaemia in asymptomatic men with normal coronary arteriograms. *Br Heart J* 1979; **41:** 214–25.

[21]Dhurandhar RW, Watt DL, Silver MD, Trimble AS, Adelman AG. Prinzmetal's variant form of angina with arteriographic evidence of coronary arterial spasm. *Am J Cardiol* 1972; **30:** 902–5.

[22]Kerin N, Macleod CA. Coronary artery spasm associated with variant angina pectoris. *Br Heart J* 1974; **36:** 224–7.

[23]Chahine TA, Raizner AE, Ishimori T, Luchi RJ, McIntosh HD. The incidence and clinical implications of coronary artery spasm. *Circulation* 1975; **52:** 972–8.

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Br Heart J 1980; **44**: 67–74

Haemodynamic and electrocardiographic effects of frusemide during supine exercise in patients with angina pectoris

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SUMMARY The influence of frusemide on haemodynamic, electrocardiographic, and symptomatic response to exercise was studied in 19 patients with documented coronary artery disease. During the control exercise period all patients experienced angina and showed ST segment depression, accompanied by raised pulmonary artery wedge pressures (PWP). In 12 of these patients 40 mg frusemide was administered intravenously and in the other seven patients 40 mg frusemide was given orally. After significant diuresis (>400 ml), the exercise test was repeated. Data were collected at the same exercise work load and duration as had been achieved before frusemide.

Both in the intravenous and oral group there was a reduction in cardiac output at rest and a less obvious reduction during exercise. The PWP during exercise after intravenous frusemide decreased from 32·9 to 11·8 mmHg and after oral frusemide from 30·7 to 15·7 mmHg. During the control period there was evidence of mitral regurgitation in seven of the patients during angina, as shown by high amplitude v waves in the PWP recordings. These alterations disappeared completely after the administration of frusemide. Ischaemic ST depression improved in 15 of 19 patients after frusemide (0·21 vs 0·09 mV). Furthermore, there was a reduction of complete suppression of anginal pain in 18 of 19 patients. Ten patients were capable of continuing exercise for a further period of time at the same work load.

These data, demonstrating the antianginal properties of frusemide, may be explained by the reduction in ventricular volumes and pressures, resulting in a decrease in myocardial wall stress and oxygen demand. The effects may be the result of both the diuretic action of frusemide and its venodilator capacity.

Frusemide has been extensively used in the treatment of heart failure and its effects on cardiovascular dynamics in failure are well established.[1–3] Clinical relief of symptoms of pulmonary congestion frequently precedes any demonstrable diuretic effect, suggesting that extrarenal factors may also be involved.[4 5] More recent studies on the extrarenal action of frusemide showed an increase of venous capacitance as an early haemodynamic effect of the drug.[6]

Little is known, however, about the effects of diuretics in patients with left ventricular dysfunction secondary to myocardial ischaemia. Dikshit *et al.*[7] suggested that similar haemodynamic changes may occur after frusemide and glyceryl trinitrate in patients with acute myocardial infarction. The clinical observation of Wilkins,[8] and Hollander *et al.*[9] that administration of diuretic agents may be associated with amelioration of anginal pain, have prompted us to study the possible role of frusemide in patients with typical exercise-induced angina pectoris. Spontaneous changes in the course of coronary artery disease may obscure the effects of any drug intervention after sustained oral treatment in patients with angina pectoris. For this reason, a single dose was used to assess the effectiveness of intravenous and oral frusemide in patients with angina pectoris and documented coronary artery disease not in clinical heart failure. Because

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of the subjective nature of antianginal response alone, emphasis is placed on the influence of the drug on haemodynamic variables and on ischaemic ST depression.

Subjects and methods

Nineteen patients, aged 42 to 61 years (average 52 years), with coronary artery disease and stable exercise-induced angina pectoris were studied. All patients had either a history of clearly documented myocardial infarction (eight subjects) and/or angiographic proof of more than 70 per cent narrowing in at least one major coronary artery. None had received diuretic drugs, antihypertensive agents, nitrates, or beta blocking agents within 48 hours before examination. The history of anginal pain ranged from six months to eight years and was induced by physical exercise in all patients. None had clinical or radiological evidence of cardiac enlargement or failure, valvular heart disease, or arrhythmias. Informed consent was obtained from each patient.

Thirty minutes before the study period, all subjects exercised at a work load comparable to that of the following main exercise periods. This allowed us to observe the patients' response, the potential occurrence of rhythm disturbances, and also to attenuate the influence of previous exercise *per se* on the haemodynamics during the study period.

Right heart catheterisation was performed without premedication using Swan-Ganz flow-directed catheters for the simultaneous determination of right atrial pressure, pulmonary artery pressure, or pulmonary artery wedge pressure. Pulmonary artery wedge pressure was considered as a reasonable approximation to left ventricular filling pressure.[10] Cardiac output was determined in triplicate by means of the thermal dilution technique with the same catheter equipment.[11 12] Systemic blood pressure was recorded either by introducing polyethylene cannulae percutaneously into a brachial artery (10 cases) or by a sphygmomanometer (nine cases). All intravascular pressures were determined with a Statham strain gauge from a zero reference level 6 cm below the angle of Louis and averaged over 10 heart cycles. The pressures and the praecordial electrocardiographic leads V4 to V6 were monitored on an oscilloscope throughout the study and recorded simultaneously at a paper speed of 50 mm/s on a multichannel recorder. ST segment depression was measured during the maximal horizontal or downsloping displacement below the level of the PR interval.

Following recordings of the resting values the patients performed supine leg exercise on a bicycle ergometer at a constant, individualised work load previously determined to evoke angina consistently within three to six minutes. The pressure recordings and electrocardiograms were repeated during exercise at one minute intervals and during the exercise angina episode. The exercise value of cardiac output was measured during the final minute of exercise, when the patients indicated the presence of definite chest pain. The patients were familiar with describing the degree of chest pain as "mild", "moderate", or "severe" from previous examinations.

After completion of the control study period 40 mg frusemide were given intravenously to 12 patients and 40 mg oral frusemide to seven patients. Within 25 minutes after intravenous administration of the drug, all patients in this group micturated spontaneously more than 400 ml urine. At this time each patient was restudied in an identical manner. In the oral group the post-frusemide study was performed 50 to 90 minutes (average 61 minutes) after administration, depending on the time of spontaneous micturition of more than 400 ml urine. Data were collected at the same exercise work load and duration as during the control study period. Those patients who were free of complaints and capable of continuing exercise were asked to do so at the same level of work load for a further period of time. Pressure values, as in the pre-frusemide study, were obtained at one minute intervals during exercise. Exercise cardiac output in the post-frusemide study was measured at the same time as during exercise before frusemide, irrespective of the presence or absence of angina pectoris.

Statistical analysis of the data was carried out using paired Student's t test.

Results

(A) HAEMODYNAMIC STUDIES

The haemodynamic response to intravenous and oral frusemide is presented in Fig. 1 to 3. Left ventricular filling pressure, as reflected by the mean pulmonary artery wedge pressure (PWP), decreased slightly at rest. Before frusemide, a precipitous increase in PWP was observed during exercise in all but one patient. After frusemide, at the same exercise duration as before the drug, there was a striking decrease of exercise PWP by 64 per cent in the intravenous group (32·9 ± 11·1 mmHg vs. 11·8 ± 5·5 mmHg, $p < 0{\cdot}001$) and by 49 per cent in the oral group (30·7 ± 5·4 mmHg vs. 15·7 ± 9·1 mmHg, $p < 0{\cdot}01$). Values of PWP in patients receiving intravenous frusemide are shown in detail in Fig. 3. Each of the 12 subjects showed a reduction in exercise PWP after frusemide.

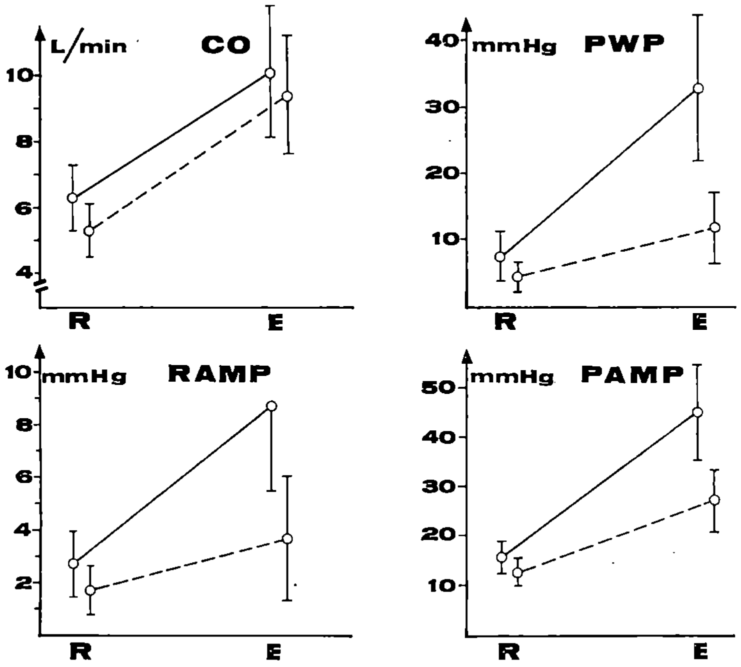


Fig. 1 *Mean values of cardiac output (CO), pulmonary artery wedge pressure (PWP), right atrial mean pressure (RAMP), and pulmonary artery mean pressure (PAMP) of 12 patients with coronary artery disease during the control study period (solid lines) and the haemodynamic response to* intravenous *frusemide (interrupted lines) at rest* (R) *and during exercise* (E).

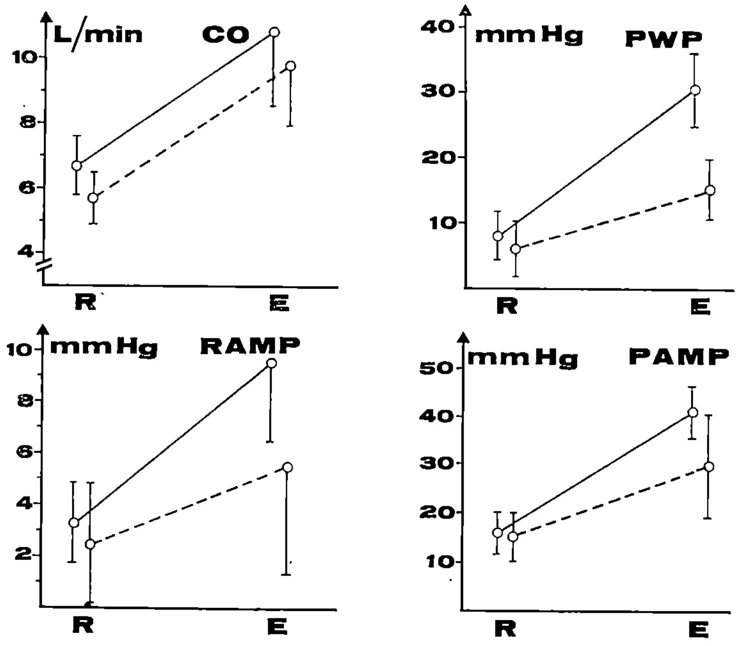


Fig. 2 *Control values (solid lines) and haemodynamic response to* oral *frusemide (interrupted lines) in seven patients with coronary artery disease. Same abbreviations as in Fig. 1.*

The occurrence of angina was associated with high left ventricular filling pressures in all but one patient in the pre-frusemide exercise test. Usually the rise of left ventricular filling pressure preceded the beginning of anginal pain. After frusemide administration, filling pressures were lower in all cases throughout the study. When angina was encountered in the post-frusemide exercise test, PWP was higher than in patients without angina, though angina clearly was produced at lower filling pressures compared with the pre-frusemide examination (Fig. 3).

Right ventricular filling pressure, as reflected by right atrial mean pressure (RAMP), also decreased slightly at rest. During exercise, at the same exercise duration as before frusemide, RAMP in the intravenous group decreased from 8·7 ±3·3 mmHg to 3·7 ±2·4 mmHg ($p < 0{\cdot}001$) and in the oral group from 9·5 ±3·0 mmHg to 5·6 ±4·3 mmHg ($p < 0{\cdot}01$).

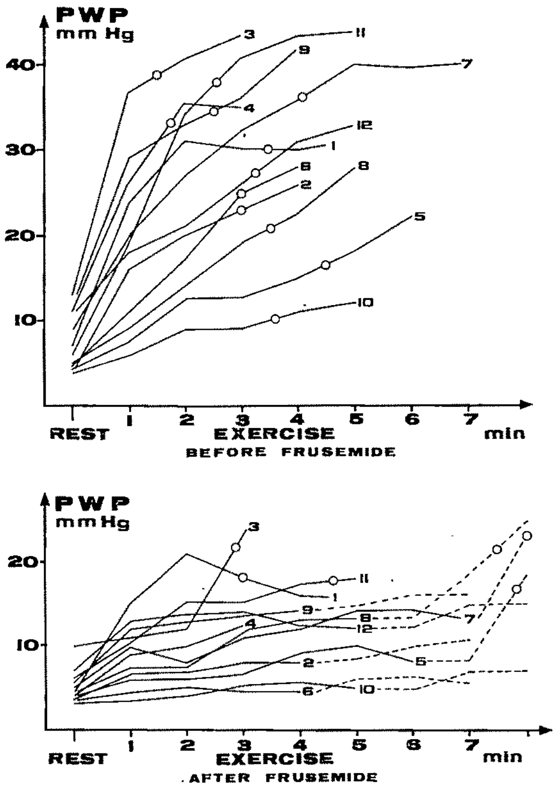


Fig. 3 *Individual values of pulmonary artery wedge pressure (PWP) at rest and at one minute intervals during exercise before and after 40 mg intravenous frusemide. The circles indicate the occurrence of angina pectoris. For comparison of data before and after frusemide, the curves of the 12 patients are marked with corresponding numbers. Patients free of symptoms after frusemide at the same exercise duration continued exercising for a further period of time (dotted lines).*

The decrease in pulmonary artery mean pressure (PAMP) was similar to the PWP reduction after frusemide. The exercise value of PAMP in the intravenous group decreased from 45·2 ±9·8 mmHg to 27·3 ±6·3 mmHg ($p < 0{\cdot}001$), and in the oral group from 40·4 ±4·7 mmHg to 31·4 ±11·3 mmHg ($p < 0{\cdot}05$).

Cardiac output at rest after intravenous frusemide fell by 16 per cent (6·3 ±1·0 l/min vs. 5·3 ±0·8 l/min, $p < 0{\cdot}001$) and after oral frusemide by 15 per cent (6·7 ±0·9 l/min vs. 5·7 ±0·8 l/min, $p < 0{\cdot}01$). The reduction in cardiac output during exercise after frusemide was 7 per cent in the intravenous group (10·1 ±2·0 l/min vs. 9·4 ±1·8 l/min, $p < 0{\cdot}005$) and after oral frusemide 10 per cent (10·9 ±2·3 l/min vs. 9·8 ±1·8 l/min, $p < 0{\cdot}01$).

During the control exercise period an increase in the v wave amplitude was observed in the PWP recordings of seven patients during angina, suggesting mitral regurgitation. These alterations disappeared completely after administration of the drug (Fig. 4a, b).

Heart rate did not change after frusemide, either at rest or during exercise. The average resting heart rate of the 19 patients was 76·3 ±13·4/min during the control period, and 75·9 ±13·9/min after frusemide; the exercise values were 114·7 ±18·9 and 113·9 ±19·1/min, respectively.

Systolic brachial artery pressure was not affected by frusemide (rest: 149·9 ±24·0 mmHg vs. 150·8 ±23·4 mmHg; exercise: 194·8 ±31·1 mmHg vs. 195·9 ±32·2 mmHg). Diastolic blood pressure showed a slight, insignificant increase after frusemide (rest: 92·4 ±8·0 mmHg vs. 95·9 ±9·1 mmHg; exercise: 104·6 ±15·4 mmHg vs. 107·3 ± 12·3 mmHg).

(B) ELECTROCARDIOGRAPHIC ABNORMALITIES

The extent of electrocardiographic abnormalities is shown in Fig. 5. Maximal ischaemic ST depression during control exercise in the intravenous group was 0·20 ±0·07 mV, and decreased by 60 per cent to 0·08 ±0·04 mV in the post-frusemide exercise test ($p < 0{\cdot}001$). A similar reduction of ST depression at the same work load and duration occurred after oral administration of frusemide (0·21 ± 0·08 mV vs. 0·10 ±0·08 mV, $p < 0{\cdot}01$).

(C) ANGINA PECTORIS

During the control study period, all patients experienced mild ($n=3$), moderate ($n=8$), or severe ($n=8$) angina at a mean work load of 51 watt (range 10 to 110 watt). During exercise after frusemide 10 patients were completely free of chest pain at the same exercise duration. Three patients indicated amelioration of chest pain from "severe" to "mild", three patients from "severe" to "moderate", and two patients from "moderate" to "mild". In one patient the complaints were unchanged. Nine of the ten patients who were completely free of complaints continued exercising at the same level of work load for an average of 3·5 minutes (range 1 to 4·5 minutes). The exercise end-point in these patients was a result of angina (three patients) and exhaustion (six patients).

(D) SERUM POTASSIUM

Serum potassium levels were obtained the day before and several hours after completion of the study. No significant changes could be found after a single intravenous or oral dose of 40 mg frusemide.

There were no side effects or complications during the study.

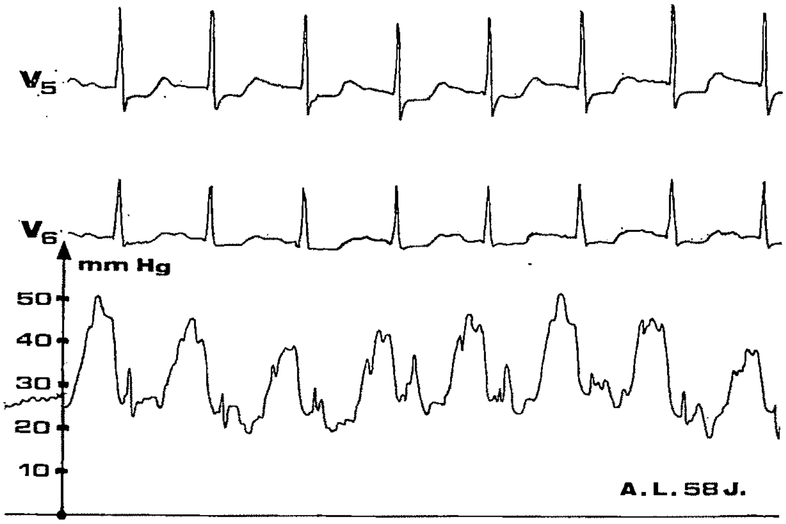
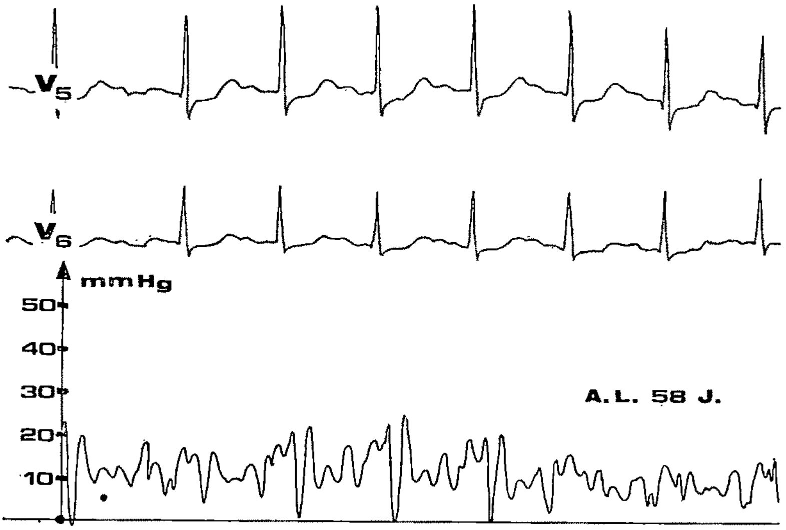


Fig. 4 (a) Upper tracing: *recordings of electrocardiographic leads V5 and V6 and simultaneous pulmonary artery wedge pressure (PWP) during severe exercise-induced angina, showing anomalous v wave amplitudes.*



(b) Lower tracing: *electrocardiogram and PWP of the same patient at identical work load after intravenous frusemide. There is a striking reduction of the PWP value and a return to normal of the v wave amplitude.*

Discussion

For the purpose of this study it was important not to accept exercise results uncritically. In fact it has been repeatedly shown that the first exercise challenge is usually a learning experience for the patient and that symptoms, pulmonary artery pressures, and other haemodynamic variables may improve during the second exercise period after repeated exercise at the same work load.[13] Therefore, repeated exercise must be interpreted with caution when studying the effect of pharmacological intervention on haemodynamics. In order to compensate for this phenomenon, an exercise study after any drug intervention should be made during the third rather than during the second exercise test.[14] This was achieved by an exercise test 30 minutes before the study period at a work load comparable to that of the following pre- and post-frusemide studies. The influence of previous exercise *per se* on the haemodynamic data during the study period is thus avoided.[14]

The present study shows that the major and most consistent effect of intravenous and oral frusemide is a prompt reduction in right and left ventricular filling pressures at the same level of exercise in patients with angina pectoris. This effect is accompanied in most patients by a reduction or complete suppression of anginal pain during exercise, in conjunction with an improvement in ischaemic ST depression. During angina many investigators have demonstrated a reduction of left ventricular compliance and contractility, resulting in an increase in filling pressure.[15–17] The increase in filling pressure is not only a consequence of myocardial ischaemia, but results in a further deterioration of oxygen supply in the ischaemic zones, and thus initiates a vicious circle.[18] These considerations suggest that any intervention aimed at reducing left ventricular filling pressure may be beneficial in the treatment of angina pectoris. It has been shown by Parker *et al.*[19] that phlebotomy during an anginal episode is of benefit in ameliorating pain; reduction of left ventricular volumes and pressures was the postulated mode of action. Likewise, the administration of diuretic agents results in a reduction of blood volume and a subsequent decrease in left ventricular dimensions and myocardial fibre length.[1–3] Since afterload (that is myocardial systolic wall tension) is a function not only of intraventricular systolic pressure but also of ventricular volume, it may be readily appreciated that a diuretic agent that reduces preload may lower afterload by reducing ventricular volume. Furthermore, the action of frusemide is not exclusively related to its diuretic properties. Rather, the immediate haemodynamic effect of the drug is primarily vascular in origin, since pronounced changes in venous capacitance could be shown, indicating a strong venous pooling effect.[6 7] The haemodynamic effects of frusemide are probably secondary to both fluid depletion and increased venous capacitance.

Our haemodynamic data strongly suggest that the "antianginal" effects of frusemide can be attributed to the unloading action of the drug. Fig. 3 shows that a steep rise in left ventricular filling pressure precedes the occurrence of anginal symptoms in most patients. After administration of frusemide the rise in filling pressures is clearly attenuated and the angina end-point delayed relative to the pre-frusemide end-point. On the other hand, angina in the post-frusemide test, though mitigated, occurred at lower filling pressures than during the control study. One patient (case 10) experienced angina at a very low filling pressure even in the pre-frusemide experiment. These latter results indicate that other mechanisms apart from left ventricular filling conditions are involved in the precipitation and termination of angina pectoris in patients with coronary artery disease.

We have plotted the changes in cardiac output against left ventricular filling pressure after frusemide to provide an approximate assessment of

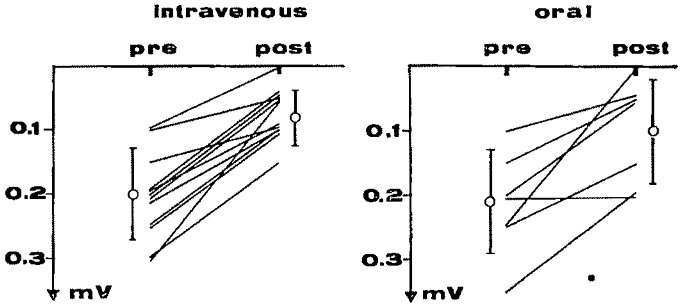


Fig. 5 *The extent of ST segment depression in the electrocardiogram during exercise before and after 40 mg intravenous, and 40 mg oral frusemide, respectively.*

left ventricular function (Fig. 6). The diagram shows only a slight reduction in cardiac output compared with large reductions in pulmonary wedge pressure in all but one patient. In this exceptional case (case 10) initial filling pressure was low in spite of severe angina, and a further decrease in left ventricular filling pressure after frusemide resulted in a substantial fall in cardiac output. Nevertheless, even this patient showed clinical improvement after frusemide. Any increase in cardiac output that might have been expected during exercise because of the improvement in myocardial ischaemia did not result, because of a pronounced reduction in pulmonary wedge pressure, reflecting a large diminution of left ventricular preload.

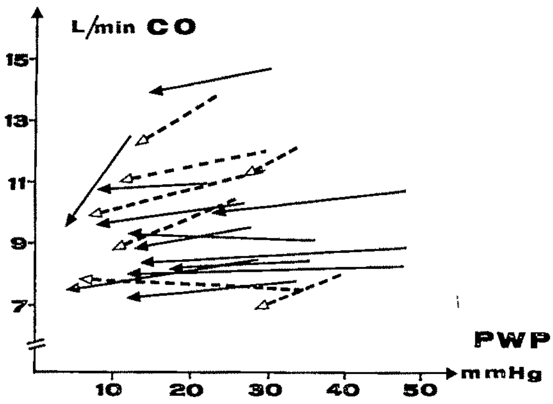


Fig. 6 *Changes in cardiac output (CO) in relation to changes in left ventricular filling pressure (PWP) during exercise after 40 mg frusemide in 19 patients with coronary artery disease (solid arrows: intravenous frusemide; interrupted arrows: oral frusemide).*

Ischaemic papillary muscle dysfunction resulting in acute mitral regurgitation is probably a common finding in coronary artery disease, at least during exertional angina.[20–22] The wedge pressure curves in seven patients during exercise were dominated by large v waves, which we interpreted as suggesting functional mitral regurgitation during severe angina.[23] Normalisation of the v wave amplitude after frusemide provides further evidence for the reduction of ischaemia by the drug.

Frusemide-induced changes in cardiac function differ from responses described with other antianginal agents. Data reported from similar studies with glyceryl trinitrate reveal that this drug decreases left ventricular end-diastolic pressure and reduces cardiac output during exercise. It also reduces systemic arterial pressure, and baroreceptor-mediated increases in heart rate tend to have opposite effects on myocardial oxygen consumption.[19 24] Beta blocking agents tend to increase left ventricular filling pressure during exercise in patients with coronary artery disease, as well as in normal subjects,[25–27] and thus may attenuate the beneficial effect on myocardial oxygen demand. In this study, frusemide improved cardiac performance, as evidenced by a shift to the left of the cardiac output/filling pressure relation, but did not induce changes in systemic blood pressure nor changes in heart rate.

It appears that the antianginal properties of frusemide are the result of reduced left ventricular volume in systole and diastole. This leads to reduced myocardial wall tension and lower myocardial oxygen requirements. Reduction of wall tension during diastole will allow for improved perfusion of the myocardium, especially of the subendocardial layers of the left ventricle. These effects are suggested as being related to the venodilator capacity of frusemide, which is later supplemented by its diuretic action.

Conclusions from these findings should be restricted to the acute symptomatic and haemodynamic response to frusemide, since maintenance diuretic therapy could have substantially different effects in patients with coronary artery disease. Therefore, as long as no controlled clinical study is available, we advocate the additional use of frusemide in patients with angina pectoris only in the presence of concomitant heart failure or hypertension. This concept is compatible with limited clinical observations[9] that administration of chlorothiazide may be associated with amelioration of the anginal syndrome in hypertensive subjects.

References

[1] Davidov M, Kakaviatos N, Finnerty FA. Intravenous administration of furosemide in heart failure. *JAMA* 1967; **200:** 824–9.

[2] Lal S, Murtagh JG, Pollock AM, Fletcher E, Binnion PF. Acute haemodynamic effects of frusemide in patients with normal and raised left atrial pressures. *Br Heart J* 1969; **31:** 711–7.

[3] Kiely J, Kelly DT, Taylor DR, Pitt B. The role of furosemide in the treatment of left ventricular dysfunction associated with acute myocardial infarction. *Circulation* 1973; **48:** 581–7.

[4] Biagi RW, Bapat BN. Frusemide in acute pulmonary oedema (letter). *Lancet* 1967; **1:** 849.

[5] Bhatia ML, Singh I, Manchanda SC, Khanna PK, Roy SB. Effects of frusemide on pulmonary blood volume. *Br Med J* 1969; **2:** 551–2.

[6] Biamino G, Wessel HJ, Schüren KP, Ramdohr B, Nöring J, Schröder R. Hämodynamische Auswirkungen von Furosemid i.v. als Ausdruck eines direkten venodilatatorischen Mechanismus (abstract). *Z Kardiol* 1974; suppl I: **63:** 51.

[7] Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJC. Renal and extra-renal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. *N Engl J Med* 1973; **288:** 1087–90.

[8] Wilkins RW. New drugs for the treatment of hypertension. *Ann Intern Med* 1959; **50:** 1–10.

[9] Hollander W, Chobanian AV, Wilkins RW. Relationship between diuretic and antihypertensive effects of chlorothiazide and mercurial diuretics. *Circulation* 1959; **19:** 827–38.

[10] Forsberg SÅ. Relations between pressure in pulmonary artery, left atrium, and left ventricle with special reference to events at end diastole. *Br Heart J* 1971; **33:** 494–9.

[11] Forrester JS, Granz W, Diamond G, McHugh Th, Chonette DW, Swan HJC. Thermodilution cardiac output determination with a single flow-directed catheter. *Am Heart J* 1972; **83:** 306–11.

[12] Nechwatal W, Eversmann A, Bier P, König E. Determination of cardiac output by means of an automatized thermal dilution technique (in German). *Klin Wochenschr* 1976; **54:** 677–82.

[13] Widimsky J, Berglund E, Malmberg R. Effect of repeated exercise on the lesser circulation. *J Appl Physiol* 1963; **18:** 983–6.

[14] Spodick DH. First and second versus second and third exercise tests (letter). *Circulation* 1975; **51:** 394.

[15] Wiener L, Dwyer EM Jr, Cox JW. Left ventricular hemodyanics in exercise-induced angina pectoris. *Circulation* 1968; **38:** 240–9

[16] Parker JO, Ledwich JR, West RO, Case RB. Reversible cardiac failure during angina pectoris. *Circulation* 1969; **39:** 745–57.

[17] Cohn PF, Gorlin R. Abnormalities of left ventricular function associated with the anginal state. *Circulation* 1972; **46:** 1065–78.

[18] Arborelius M Jr, Lecerof H, Malm A, Malmborg, RO. Acute effects of nitroglycerin on haemodynamics of angina pectoris. *Br Heart J* 1968; **30:** 407–11.

[19] Parker JO, Case RB, Khaja F, Ledwich JR, Armstrong PW. The influence of changes in blood volume on angina pectoris: a study of the effect of phlebotomy. *Circulation* 1970; **41:** 593–604.

[20] Brody W, Criley JM. Functional mitral regurgitation (letter). *N Engl J Med* 1968; **279:** 1058.

[21] Burch GE, DePasquale NP, Phillips HJ. The syndrome of papillary muscle dysfunction. *Am Heart J* 1968; **75:** 399–415.

[22] Shelbourne JC, Rubinstein D, Gorlin R. A reappraisal of papillary muscle dysfunction. *Am J Med* 1969; **46:** 862–71.

[23] Malmborg RO. Physiological signs of incipient cardiac insufficiency in ischemic heart disease. In: *Incipient cardiac insufficiency. Symposium of the European Society of Cardiology, Locarno,* 1970: 89.

[24] Clausen JP, Trap-Jensen J. Heart rate and arterial blood pressure during exercise in patients with angina pectoris. Effects of training and of nitroglycerin. *Circulation* 1976; **53:** 436–42.

[25] Parker JO, West RO, Di Giorgi S. Hemodynamic effects of propranolol in coronary heart disease. *Am J Cardiol* 1968; **21:** 11–19.

[26] Dunér H, Pernow B. Haemodynamic effects of β-receptor blocking agents and digitalis in ischaemic coronary heart disease with angina pectoris. *Acta Med Scand* 1973; **194:** 517–23.

[27] Nechwatal W, König E, Isbary Greding H. Hemodynamic interaction of propranolol and digitalis in patients with arterial hypertension (in German). *Z Kardiol* 1977; **66:** 572–7.

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Effect of isoprenaline and propranolol on left ventricular function as determined by nuclear angiography

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SUMMARY We have studied changes in left ventricular function with non-invasive nuclear angiography, at rest, during graded infusions of isoprenaline (0·75, 1·0, and 2·0 μg/min), and 10 minutes after a single intravenous injection of propranolol (0·25 mg/kg). To test the adequacy of beta-adrenoreceptor antagonism, isoprenaline (2·0 μg/min) was reinfused after propranolol. Eight healthy subjects have been studied.

Ventricular volume-time curves were obtained by electrocardiogram-gated accumulation of count rates in sequential 20 ms time bins (over 500 cardiac cycles) from a selected region of interest corresponding to the left ventricular blood pool. ^{99m}Tc-HSA was used as the radiopharmaceutical. In addition to the ejection fraction, the mean ejection rate, peak rate of change of volume in systole and diastole, and the mean ejection and filling times were calculated from these volume-time curves. A linear dose dependance has been shown in the changes in ejection fraction, mean ejection rate, peak rate of change of volume in systole, and mean ejection time. After beta-adrenoreceptor antagonism the resting values of various variables were not significantly different from the control values, except for the mean ejection rate. Reinfusion of isoprenaline after beta-adrenoreceptor antagonism was without effect on any of the variables.

This study shows that nuclear angiography provides a satisfactory non-invasive technique for the evaluation of cardiac function, especially when physiological and pharmacological interventions are examined.

Changes in ventricular volume can be measured at nuclear angiography by imaging a suitably labelled blood pool within the heart using a gamma camera system. The electrocardiogram-gated accumulation of radioactivity in sequential time bins yields an activity-time curve from which complementary variables of ventricular function may be measured. Since count rates within the region being sampled are proportional to volume, it is implied that such activity-time curves represent proportional volume change. A good correlation between the ejection fraction measured by this technique and that measured by contrast cineangiography has been reported earlier from this laboratory[1] and also by other workers.[2–4] A distinct advantage of this method is that repeated measurements can be made over a period of at least four hours while physiological and pharmacological interventions are being tested. Furthermore, it is possible to undertake longitudinal investigation of ventricular function in the same patient without undue discomfort.

In order to define the value of this technique in the clinical assessment of cardiac function and, more importantly, sequential changes in cardiac function, we report on the effect of positive inotropic stimulation with infusions of graded doses of isoprenaline and negative inotropic intervention with propranolol in a group of healthy subjects.

Subjects and methods

These studies were carried out in eight healthy subjects drawn from a routine referral service for the investigation of acute chest pain. All subjects had a history of vague chest pain thought to be non-ischaemic in origin. They also had normal findings

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on a detailed clinical examination, resting and exercise electrocardiograms (to a workload of 900 kpm), and chest *x*-ray films. Informed consent was obtained from all subjects and the study had the approval of our hospital ethical committee.

The patients were studied in the supine position. Possible thyroid uptake was blocked by two doses of potassium iodide given orally during the preceding 24 hours.

Cardiac blood pool imaging was performed in the 30° left anterior oblique projection with a 10° caudal tilt using a Nuclear Enterprises Mk 5 HR gamma camera fitted with a high resolution parallel-hole collimator. Between 12 and 15 mCi of technetium-99m labelled to human serum albumin was injected into the left antecubital vein through an indwelling cannula and flushed in rapidly with a single 20 ml bolus of normal saline.

After resting measurements for 10 minutes, constant rate infusions of isoprenaline were given and cardiac imaging was continued. Three sequential incremental steps of isoprenaline infusion in the dose of 0·75, 1, and 2 µg/min were used. Each dose level was maintained for approximately 10 minutes. After this, beta-adrenoreceptor antagonism was produced with a single bolus of 0·25 mg/kg body weight of propranolol and the recordings repeated after a 10-minute wait. Lastly, isoprenaline infusion at a dose of 2 µg/min was restarted while the measurements were continued.

During the procedure the electrocardiogram from a display unit, heart rate from a digital counter connected to the electrocardiograph, and blood pressure by sphygmomanometry were monitored continuously. The data from the gamma camera, together with a bipolar electrocardiogram derived from the chest leads, were recorded simultaneously in analogue form on videotape.

The ventricular volume curves were generated during replay of the data from the videotapes.[1] A region of interest corresponding to the left ventricle was selected on the gamma camera. Care was taken to exclude the left atrium and the right ventricle from the selected field of view. For measurement of background a crescentic area was defined either just inside or just outside the lateral and inferior margins of the selected left ventricular region. The counts from these two areas were accumulated in sequential 20 ms time intervals throughout each cardiac cycle beginning with the peak of the R wave on the accompanying electrocardiogram. Approximately 500 consecutive cardiac cycles were sampled for each measurement. The left ventricular region of interest was checked after each intervention in order to avoid errors caused by changes in the end-diastolic volume.

The count rates, along with the RR interval histogram, were transferred to a PDP 12 computer and ventricular volume curves plotted. The digital filtering technique to filter out the high-frequency noise from the raw data is described elsewhere.[5] Volume curves showing a standard deviation of the RR interval of greater than 60 ms were rejected. Corrections were made for background counts and the ejection fraction (EF) was calculated.[1] The volume curve was differentiated to give the peak rate of change of volume in systole (dV_s/dt) and diastole (dV_d/dt). Mean times of ejection ($\bar{t}_s$) and filling ($\bar{t}_d$) were calculated from the ventricular curve according to the general equation:

$$\bar{t} = \frac{\Sigma(V_i - V_{i+1}) \cdot \frac{(t_i + t_{i+1})}{2}}{\Sigma(V_i - V_{i+1})}$$

for values of t_i throughout each phase of the cardiac cycle where V_i is the relative volume at time t_i.

As a weighted mean these times represent the centre of gravity of the corresponding segments of the differentiated volume curve. In order to study the effect on $\bar{t}_s$ and $\bar{t}_d$ values as a result of changes in the cycle length alone, without changes in inotropy, measurements were made at rest and at peak heart rates after each of two successive injections of atropine (600 µg each). The volume time curves for this purpose were obtained in a similar manner in another six patients recovering from a myocardial infarction.

The left ventricular ejection time (LVET) was measured from the volume-time curve as the interval between the end-diastolic and end-systolic channels. The mean ejection rate was calculated as EF/LVET. The volume curve was normalised to the end-diastolic volume so that the units for various indices, that is peak rate of volume change during systole (dV_s/dt) and diastole (dV_d/dt) and the mean ejection rate are expressed as end-diastolic volumes per second (ED vol/s). Statistical comparisons were made by the Student's t test for paired data.

Results

The mean data for all subjects are given in Table 1. The heart rate increased from a resting average of 78 beats per min to 106 beats per min at the maximum dose of isoprenaline used. The systolic blood pressure increased slightly (+13·0%) and the diastolic blood pressure decreased somewhat

(– 8·7%), resulting in the characteristic widening of the pulse pressure during infusions of isoprenaline (Fig. 1). Fig. 2 shows the ventricular volume curves at rest and after each of the pharmacological interventions in one patient. For all subjects the ejection fraction at rest averaged 0·58 ±0·06 (SD) and increased to 0·70 ±0·09 (SD) at an infusion rate of 0·75 μg/min (Iso 1), 0·72 ±0·10 (SD) at an infusion rate of 1 μg/min (Iso 2), and 0·76 ±0·08 (SD) at an infusion rate of 2·0 μg/min (Iso 3). After beta-adrenoreceptor antagonism the mean ejection fraction of 0·52 ±0·07 (SD) was not significantly different from the resting values. Reinfusion of isoprenaline at 2·0 μg/min was now without effect (Fig. 3).

The changes in mean ejection rate were similar with increases of 45, 57, and 97 per cent during incremental doses of isoprenaline. After propranolol mean ejection rate was significantly lower (14%, $p < 0·02$) than in the control period, and remained unchanged when 2 μg/min of isoprenaline was reinfused (Fig. 3).

With increasing doses of isoprenaline infusion dV_s/dt increased progressively by 18, 28, and 63 per cent relative to the resting value (Fig. 4). After propranolol the mean value was not significantly different from that at rest and no significant change was seen on reinfusion of isoprenaline at a dose rate of 2·0 μg/min. The changes in dV_d/dt were somewhat variable and did not achieve statistical significance.

The mean ejection time ($\bar{t}_s$) declined progressively

Table 1 *Changes in left ventricular function after beta-adrenergic stimulation with isoprenaline and beta-adrenoreceptor antagonism with propranolol*

Variable *Dose of drug*	*Rest* *0*	*Iso-1* *(0·75 μg/min)*	*Iso-2* *(1 μg/min)*	*Iso-3* *(2 μg/min)*	*Prop.* *(0·25 mg/kg)*	*Prop + Iso-3* *(2 μg/min)*
No. of subjects	8	7	7	8	6	6
BP systolic (mmHg)	118 ±1·8*	124 ±2·3 (<0·02)	126 ±2·3 (<0·001)	133 ±3·2 (<0·001)	118 ±2·0 (>0·2)	121 ±2·4 (>0·2)
BP diastolic (mmHg)	69 ±1·8	64 ±1·5 (<0·05)	63 ±1·1 (<0·02)	64 ±1·8 (<0·05)	76 ±2·9 (<0·02)	79 ±3·2 (<0·02)
Heart rate per min	78·3 ±2·90	86·4 ±2·88 (<0·01)	92·0 ±3·28 (<0·01)	106·0 ±4·09 (<0·001)	66·7 ±2·21 (<0·01)	64·6 ±3·07 (<0·01)
LVET (ms)	303 ±5·52	254 ±7·79 (<0·01)	237 ±7·33 (<0·001)	204 ±7·49 (<0·001)	317 ±3·04 (>0·05)	313 ±6·09 (>0·1)
LVFT (ms)	473 ±23·89	443 ±18·69 (<0·05)	429 ±19·19 (<0·01)	370 ±17·04 (<0·01)	579 ±23·24 (<0·01)	588 ±36·91 (<0·05)
Ejection fraction	0·58 ±0·02	0·70 ±0·03 (<0·01)	0·72 ±0·04 (<0·001)	0·76 ±0·03 (<0·001)	0·52 ±0·03 (>0·2)	0·53 ±0·03 (>0·2)
Mean ejection rate (ED vol/s)	1·92 ±0·10	2·78 ±0·20 (<0·01)	3·02 ±0·26 (<0·001)	3·78 ±0·26 (<0·001)	1·65 ±0·10 (<0·02)	1·67 ±0·13 (<0·05)
dV_s/dt (ED vol/s)	5·98 ±0·26	7·07 ±0·27 (<0·05)	7·65 ±0·31 (<0·05)	9·74 ±0·33 (<0·001)	6·18 ±0·31 (>0·1)	5·59 ±0·31 (>0·7)
dV_d/dt (ED vol/s)	5·65 ±0·35	5·73 ±0·41 (>0·8)	5·64 ±0·22 (>0·6)	6·43 ±0·27 (>0·05)	5·20 ±0·22 (>0·2)	5·14 ±0·40 (>0·6)
$\bar{t}_s$ (ms)	156 ±3·7	116 ±3·9 (<0·001)	112 ±5·3 (<0·001)	94 ±3·8 (<0·001)	158 ±3·0 (>0·3)	159 ±3·0 (>0·2)
$\bar{t}_d$ (ms)	201 ±13·4	181 ±7·3 (>0·05)	165 ±7·7 (<0·01)	166 ±8·2 (<0·02)	214 ±20·3 (>0·2)	221 ±23·5 (>0·1)
$\bar{t}_s$/LVET	0·51 ±0·01	0·46 ±0·01 (<0·001)	0·47 ±0·02 (<0·05)	0·46 ±0·02 (<0·01)	0·50 ±0·01 (>0·9)	0·51 ±0·01 (>0·9)
$\bar{t}_d$/LVFT	0·43 ±0·04	0·41 ±0·01 (>0·9)	0·39 ±0·01 (>0·05)	0·45 ±0·02 (>0·9)	0·37 ±0·03 (>0·05)	0·38 ±0·03 (>0·05)

* Mean ± one standard error of the mean (SE). Figures in parentheses are the p values for the difference from corresponding resting measurement.

Iso, isoprenaline; Prop., propranolol; LVET, left ventricular ejection time; LVFT, left ventricular filling time; dVS/dt and dV_d/dt, peak rate of change of volume in systole and diastole; $\bar{t}_s$ and $\bar{t}_d$, mean times of ejection and filling; ED vol/s, end-diastolic volumes per second.

with increasing doses of isoprenaline from 156 ± 10 ms (SD) at rest to 94 ± 11 ms (SD) at the maximum dose of isoprenaline infusion. It returned to resting values after propranolol, with no significant change on reinfusion of 2 µg/min of isoprenaline (Fig. 4). The effect of cycle length alone on $\bar{t}_s$ and $\bar{t}_d$ was examined from data obtained at rest and after each of two successive injections of atropine. The correlation coefficient between $\bar{t}_s$ and LVET was 0·41 ($p > 0{\cdot}05$) and between $\bar{t}_d$ and the left ventricular filling time (LVFT) this was 0·35 ($p > 0{\cdot}1$) over heart rates ranging from 63 to 121 beats per min (80·7 ± 13·9 SD). The $\bar{t}_s$/LVET ratio was 0·54 at rest and did not change significantly after injections of atropine, while the $\bar{t}_d$/LVFT ratio increased progressively with the increase in heart rate (Table 2). After injection of isoprenaline the correlation coefficient between $\bar{t}_s$ and LVET was 0·90 ($p < 0{\cdot}001$) and between $\bar{t}_d$ and LVET this was 0·58 ($p < 0{\cdot}02$). A similar but negative correlation was found between $\bar{t}_s$ and EF after isoprenaline ($r = -0{\cdot}77$, $p < 0{\cdot}001$). The correlation between $\bar{t}_d$ and EF was not significant ($r = 0{\cdot}36$, $p > 0{\cdot}1$). The $\bar{t}_s$/LVET ratio decreased from 0·51 at rest to 0·46 after isoprenaline (Table 1). The $\bar{t}_d$/LVET ratio showed variable and insignificant changes. After beta-adrenoreceptor antagonism with or without reinfusion of isoprenaline the values of $\bar{t}_s$, t_d, and $\bar{t}_s$/LVET were not significantly different from the control values. However, $\bar{t}_d$/LVFT ratio was significantly reduced (Table 1.)

Discussion

Until recently the only available methods for the measurement of dynamic changes in ventricular

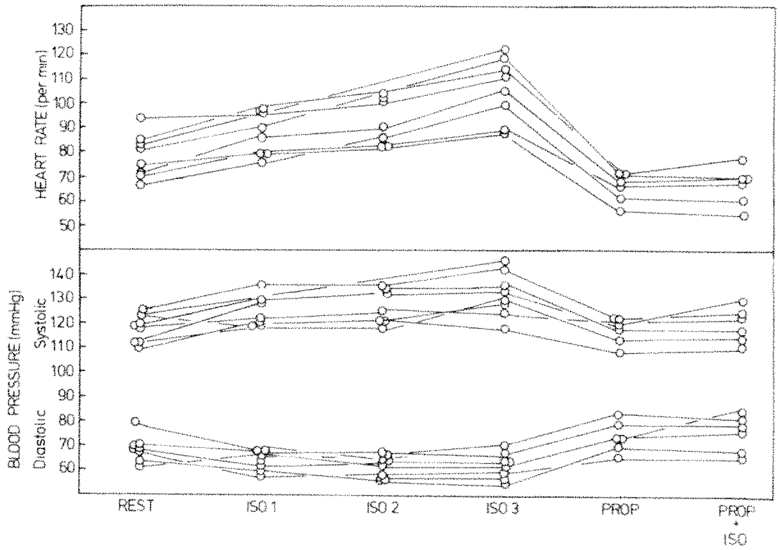

Fig. 1 *Heart rate and blood pressure changes with increasing doses of isoprenaline and after beta adrenoreceptor antagonism with propranolol.*

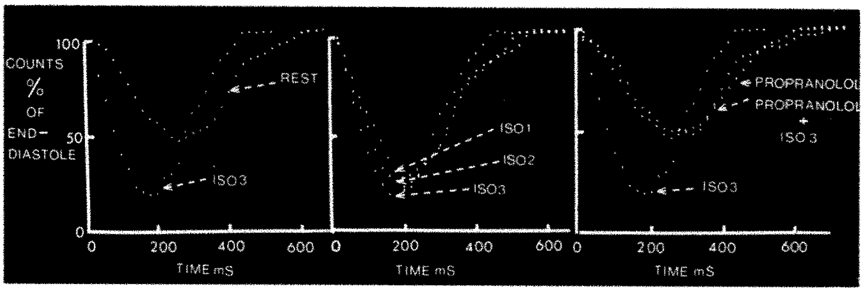

Fig. 2 *Ventricular volume curves in one subject at rest and after each of the drugs. Each curve has been accumulated over 500 cardiac cycles and the count rates are expressed as a percentage of the end-diastolic counts. The time on the abscissa is from the peak of the R wave on the electrocardiogram.*

volume in man required either contrast angiography[6 7] or the implantation at surgery of radio-opaque markers.[8] The limitations of single probe TM echocardiography, both on theoretical and practical grounds, are now well recognised.[9–11] Nuclear angiography provides a useful alternative method, especially when sequential measurements are desired.

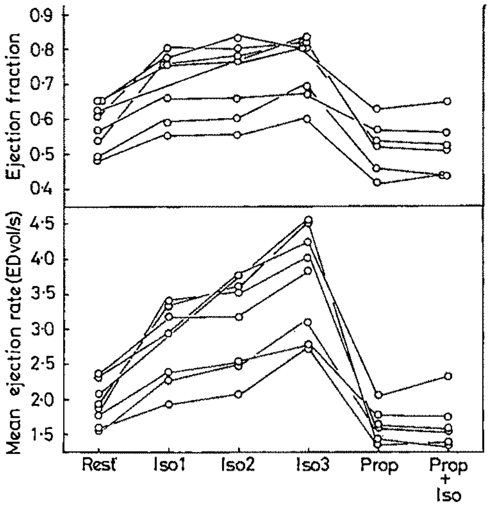

Fig. 3 *Changes in ejection fraction and mean ejection rate in individual subjects.*

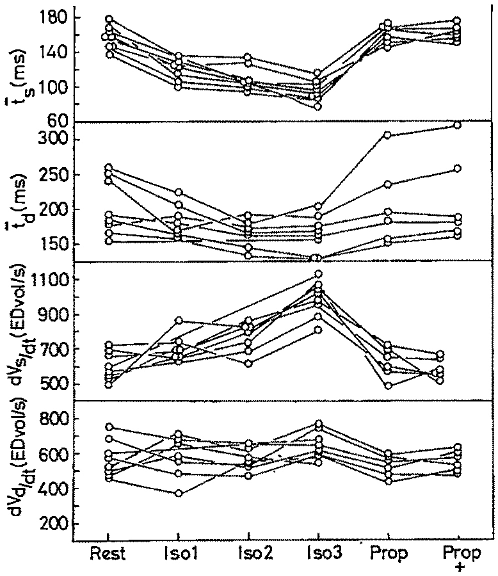

Fig. 4 *Changes in the indices of rate of change of volume in systole and diastole with increasing doses of isoprenaline before and after beta adrenoreceptor antagonism with propranolol.*

Three different approaches have been used for the study of global volume changes by nuclear angiography. Time-activity curves obtained during the first pass of a radioactive bolus[5 12 13] have the advantage of a low background, but the disadvantage of relatively poor counting statistics. Furthermore, measurements cannot be repeated more than once during the same study period, except perhaps when using isotopes with ultra-short half-lives. The second approach requires serial accumulations of electrocardiogram-gated images at end-systole and end-diastole; the ejection fraction is then obtained either by computer subtraction[14] or from geometric area-length analyses.[15 16] In either case only limited information about the ejection fraction is obtained. The latter method is handicapped by fallacies inherent in assumptions of ventricular geometry and ignores a major advantage of nuclear angiography. No assumptions of geometry need be made in the estimation of volume change by nuclear angiography since count density is proportional to volume.

The third approach is a modification of the second in that numerical data from gated acquisition of count rates are plotted in the form of a composite volume-time curve representing a single averaged cardiac cycle.[1 4 17 18] Not only are sequential measurements possible, but information about volume change throughout the cardiac cycle is obtained. This method was therefore chosen for the present study. Since data were accumulated over several cardiac cycles measurements were restricted to "steady state" conditions.

In the present study, drugs with known pharmacological actions were chosen to examine the confidence with which changes in myocardial function

Table 2 *Effect of atropine on $\bar{t}_s$ and $\bar{t}_d$ and related indices (mean ±SE)*

	Rest	*Atropine-1 (0·6 mg)*	*Atropine-2 (1·2 mg)*
No. of subjects	6	6	6
RR interval (ms)	853 ±35·57	760·8 ±29·19	667 ±35·47
LVET (ms)	307 ±10·19	293 ±9·03	280 ±8·17
LVFT (ms)	546 ±30·20	467 ±23·96	387 ±28·73
$\bar{t}_s$ (ms)	166 ±6·34	158 ±4·13	153 ±8·39
$\bar{t}_d$ (ms)	231 ±22·09	238 ±23·79	225 ±31·51
$\bar{t}_s$/LVET	0·54 ±0·03	0·54 ±0·02	0·55 ±0·02
$\bar{t}_d$/LVFT	0·43 ±0·05	0·51 ±0·05	0·57 ±0·05
Ejection fraction	0·45 ±0·09	0·46 ±0·08	0·47 ±0·09
Mean ejection rate (ED vol/s)	1·49 ±0·31	1·61 ±0·33	1·75 ±0·40

can be determined by nuclear angiography. The changes in heart rate and blood pressure were in keeping with the known haemodynamic response to beta-adrenergic stimulation with isoprenaline[19 20] and beta-adrenoreceptor antagonism with propranolol.[21 22] The effectiveness of beta-adrenoreceptor antagonism is testified by the absence of significant haemodynamic changes during re-infusion of isoprenaline (2 µg/min).

During infusions of isoprenaline a linear dose dependance is seen for the ejection fraction, mean ejection rate, dV_s/dt, and $\bar{t}_s$ (Fig. 5). Considering the moderate doses of isoprenaline infusions, the results suggest that changes in myocardial function can be assessed with reasonable confidence by nuclear angiography. A similar order of magnitude of changes in ejection fraction with isoprenaline have been reported previously.[23 24] Since pacing-induced tachycardia results in a decrease in ejection fraction (15% decrease in ejection fraction for a 34% increase in heart rate) and end-diastolic volume,[25] the seemingly small increases in ejection fraction during infusions of isoprenaline assume greater significance.

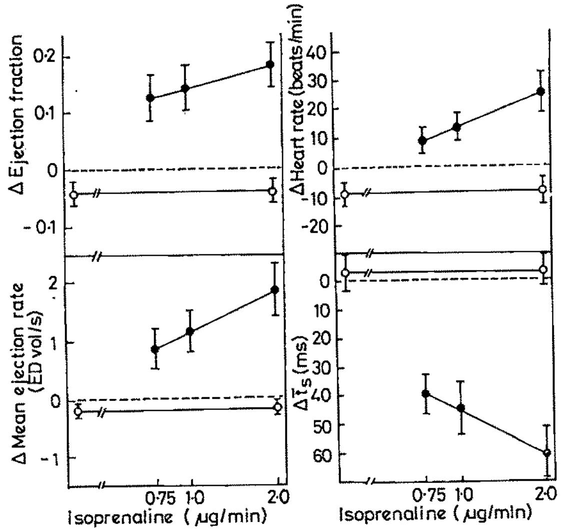

Fig. 5 *Dose response curves relating ejection fraction, mean ejection rate, heart rate, and t_s with the dose of isoprenaline plotted on a log scale. Only the mean differences from the resting values (the zero line ------) and 2 SE of the differences are shown. Closed circles are the data before beta-adrenoreceptor antagonism and show a linear response to increasing dose levels of isoprenaline. The open circles show the effects of beta-adrenoreceptor antagonism. Infusion of isoprenaline at a dose rate of 2·0 µg/min after propranolol is without effect on these variables.*

There are, however, no published data on the other variables measured in this study. Comparison with the classical experiments of Rushmer in intact unanaesthetised dogs shows similar changes in ejection velocity and rate of change of diameter after beta-adrenergic stimulation and block.[26]

The changes in peak rate of change of volume may be expected to be a more sensitive index of changes in myocardial function. This measurement, however, is very sensitive to the degree of filtering to which the data are subjected (unpublished observations). In the present studies care was taken to ensure optimal filtering but, in the absence of a precise mathematical expression that defines the indices of an optimal filter, a certain element of subjective uncertainty is likely to affect adversely the value of this variable when measured at nuclear angiography.

The mean ejection rate, as a measure of the average velocity of flow, is more sensitive than the ejection fraction to changes in the inotropic state. After beta-adrenoreceptor antagonism a small but significant decrease was found in the mean ejection rate but not in the ejection fraction. The mean ejection time ($\bar{t}_s$) represents the time taken to move 50 per cent of the total volume displaced during systole. The ratio $\bar{t}_s$/LVET therefore helps to partition the mean ejection velocity into two periods of equal volume displacement. A ratio of 0·5 indicates a symmetrical velocity profile of ejection, whereas values of less than 0·5 indicate a more rapid ejection of the first 50 per cent of the stroke volume compared with the next 50 per cent. The latter would indicate a more forceful and rapid contraction during the earlier parts of systole compared with the later phases of systole, as is expected during inotropic stimulation. In the present study graded infusions of isoprenaline resulted in a progressive shortening of $\bar{t}_s$ and a decrease in $\bar{t}_s$/LVET ratio in association with a larger stroke volume and ejection fraction. On the other hand, tachycardia induced with atropine is without effect on the $\bar{t}_s$/LVET ratio and hence the velocity profile of ejection. A significant advantage is that unlike the dV_s/dt values, $\bar{t}_s$ is not affected much by the filter bandwidth (unpublished observations).

In conclusion, therefore, volume-time curves obtained at nuclear angiography provide reasonably accurate and sensitive quantitative information about the function of the cardiac pump. As a non-invasive technique, the method is particularly suited for the study of physiological and pharmacological interventions and also longitudinal follow-up studies.

References

[1]Muir AL, Hannan WJ, Brash HM, Baldwa V, Miller HC, Ogilvie B. The assessment of left ventricular ejection fraction in patients with ischaemic heart disease by contrast ventriculography and nuclear angiography. *Clin Sci Mol Med* 1977; **53:** 55–61.

[2]Green MV, Brody WR, Douglas MA, Redwood DR, Bailey JJ, Johnston GS. Count rate measurements of left ventricular ejection fraction from gated scintigraphic images (abstract). *J Nucl Med* 1976; **17:** 557.

[3]Burow RD, Strauss HW, Singleton R, *et al.* Analysis of left ventricular function from multiple gated acquisition cardiac blood pool imaging. Comparison to contrast angiography. *Circulation* 1977; **56:** 1024–8.

[4]Folland ED, Hamilton GW, Larson SM, Kennedy JW, Williams DL, Ritchie JL. Radionuclide ejection fraction: a comparison of three radionuclide techniques with contrast angiography. *J Nucl Med* 1977; **18:** 1159–66.

[5]Hannan WJ, Hare RJ, Hughes SHC, Scorgie RE, Muir AL. Simplified method of determining left ventricular ejection fraction from a radionuclide bolus. *Eur J Nucl Med* 1977; **2:** 71–4.

[6]Dodge HT, Sandler H, Ballew DW, Lord JD Jr. Use of biplane angiocardiography for the measurement of left ventricular volume in man. *Am Heart J* 1960; **60:** 762–76.

[7]Sandler H, Dodge HT. The use of single plane angiocardiograms for the calculation of left ventricular volume in man. *Am Heart J* 1968; **75:** 325–34.

[8]Harrison DC, Goldblatt A, Braunwald E. Studies on cardiac dimensions in intact, unanaesthetized man. 1. Description of techniques and their validation. *Circ Res* 1963; **13:** 448–55.

[9]Feigenbaum H. Echocardiographic examination of the left ventricle (editorial). *Circulation* 1975; **51:** 1–7.

[10]Teichholz LE, Kruelen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence or absence of asynergy. *Am J Cardiol* 1976; **37:** 7–11.

[11]Fortuin NJ, Pawsey CGK. The evaluation of left ventricular function by echocardiography. *Am J Med* 1977; **63:** 1–9.

[12]Schelbert HR, Verba JW, Johnson AD, *et al.* Non-traumatic determinations of left ventricular ejection fraction by radionuclide angiocardiography. *Circulation* 1975; **51:** 902–9.

[13]Myers RW. Single transit non-gated radionuclide angiocardiography for assessing left ventricular wall motion and ejection fraction. *Clin Nucl Med* 1976; **1:** 191–7.

[14]Secker-Walker RH, Resnick L, Kunz H, Parker JA, Hill RL, Potchen EJ. Measurement of left ventricular ejection fraction. *J Nucl Med* 1973; **14:** 798–802.

[15]Sullivan RW, Bergeron DA, Vetter WR, Hyatt KH, Haughton V, Vogel JM. Peripheral venous scintillation angiocardiography in determination of left ventricular volume in man. *Am J Cardiol* 1971; **28:** 563–7.

[16]Strauss HW, Zaret BL, Hurley PJ, Natarajan TK, Pitt B. A scintiphotographic method for measuring left ventricular ejection fraction in man without cardiac catheterisation. *Am J Cardiol* 1971; **28:** 575–80.

[17]Bacharach SL, Green MV, Borer JS, Douglas MA, Ostrow HG, Johnston GS. A real-time system for multi-image gated cardiac studies. *J Nucl Med* 1977; **18:** 79–84.

[18]Bacharach SL, Green MV, Borer JS, Ostrow HG, Redwood DR, Johnston GS. ECG-gated scintillation probe measurement of left ventricular function. *J Nucl Med* 1977; **18:** 1176–83.

[19]Dodge HT, Lord JD, Sandler H. Cardiovascular effects of isoproterenol in normal subjects and subjects with congestive heart failure. *Am Heart J* 1960; **60:** 94–105.

[20]Krasnow N, Rolett EL, Yurchak PM, Hood WB Jr, Gorlin R. Isoproterenol and cardiovascular performance. *Am J Med* 1964; **37:** 514–25.

[21]Epstein SE, Robinson BF, Kahler RL, Braunwald E. Effects of beta-adrenergic blockade on the cardiac responses to maximal and sub-maximal exercise in man. *J Clin Invest* 1965; **44:** 1745–53.

[22]Macdonald HR, Sapru RP, Taylor SH, Donald KW. Effect of intravenous propranolol on the systemic circulatory response to sustained handgrip. *Am J Cardiol* 1966; **18:** 333–43.

[23]Harrison DC, Glick G, Goldblatt A, Braunwald E. Studies on cardiac dimensions in intact, unanesthetized man. IV. Effects of isoproterenol and methoxamine. *Circulation* 1964; **29:** 186–94.

[24]Hinds JE, Hawthorne EW. Comparative cardiac dynamic effects of dobutamine and isoproterenol in conscious instrumented dogs. *Am J Cardiol* 1975; **36:** 894–901.

[25]Ricci DR, Ingels NB Jr, Daughters GT II, Stinson EB, Alderman EL. Intrinsic relationship of heart rate and ejection fraction in man (abstract). *Circulation* 1976; **53 & 54,** suppl II: 31.

[26]Van Citters RL, Baker D, Rushmer RF. Cardiac adrenergic blockade with DCI in the intact unanesthetized animal. *Am J Physiol* 1961; **200:** 990–4.

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Br Heart J 1980; **44:** 82–90

Electrophysiological assessment of amiodarone in treatment of resistant supraventricular arrhythmias*

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SUMMARY Oral amiodarone has been used to treat 21 patients with various supraventricular arrhythmias; 13 had Wolff-Parkinson-White syndrome, which was complicated by atrial fibrillation and re-entry atrioventricular tachycardia in four, and re-entry tachycardia alone in the other nine. The remaining eight patients had paroxysmal atrial fibrillation or flutter without pre-excitation. All were refractory to conventional treatment and had undergone intracardiac electrophysiological study. Fifteen have been controlled with amiodarone, this treatment proving most effective in atrial fibrillation or flutter with or without pre-excitation. Amiodarone was successful in only four of the nine patients with re-entry atrioventricular tachycardia. In two patients who responded well the drug had to be discontinued because of side effects.

Despite the abundance of drugs available for the prophylaxis of supraventricular arrhythmias there are some patients in whom conventional antiarrhythmic medications fail. While surgery is feasible in these resistant cases[1] it is usually reserved for life-threatening arrhythmias. Amiodarone, a benzfuran derivative originally introduced as an antianginal agent,[2] has been shown to be effective in a wide variety of supraventricular arrhythmias[3–5] including those complicating pre-excitation.[6 7] Subsequent reports, however, have not confirmed the original high success rates.[7 8]

Though relatively little is known of its pharmacological behaviour, there is evidence that amiodarone is slowly absorbed,[9] has a long half-life,[10] and a persistent action.[5] Its antiarrhythmic action appears to differ when given intravenously as opposed to orally.[4] We investigated the action of oral amiodarone in 21 patients with supraventricular arrhythmias after electrophysiological study had been performed to define the precise nature of arrhythmia. All were evaluated during treatment by repeated 24-hour ambulatory electrocardiographic monitoring. Limited electrophysiological testing was performed during treatment in nine of the patients with the Wolff-Parkinson-White syndrome. The results were then compared with symptoms during the follow-up period (three to 25 months). The repeat electrophysiological studies provided further information on the therapeutic efficacy of amiodarone and its range of action, and clarified why it failed in some.

Methods

Twenty-one patients, all with a history of recurrent palpitation, underwent intracardiac electrophysiological testing to determine the nature of their arrhythmias. The studies were performed according to our standard procedure[11] with modifications discussed below. Each study was performed in the fasting state after informed consent had been obtained and after all medications had been stopped for at least 72 hours.

Electrodes for stimulation and recording were positioned in the high right atrium, close to the septal cusp of the tricuspid valve, and at the apex of the right ventricle. A fourth electrode was used for atrial endocardial mapping and to allow stimulation from atrial sites other than the high right atrium. The recordings obtained were led via isolated selection boxes to the high-gain amplifiers (15 to 1200 Hz) of an ink-jet recorder and displayed at a paper speed of 100 mm/s, together with surface electrocardiograph leads I, III, V1, and V6. All information was recorded on a high-fidelity multichannel tape recorder for later retrieval. Stimulation studies were performed using a programmable

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stimulator (Devices 4971) delivering impulses of 2 ms duration at twice diastolic threshold.

The following electrophysiological measurements were made during the study.

(1) Corrected sinus node recovery time after high right atrial pacing for one minute at 80, 120, and 140 stimuli a minute.[12]

(2) Effective refractory periods of atrial and ventricular myocardium.

(3) Effective refractory period and functional refractory period of the atrioventricular node in the anterograde direction and the refractory periods of any other anterogradely functioning atrioventricular pathway. The values for the atrioventricular node were determined by the introduction of premature stimuli in the high right atrium. In the presence of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) pacing was performed as close as possible to the atrial insertion of the pathway, as determined by atrial mapping during ventricular pacing or induced orthodromic reciprocating atrioventricular tachycardia (in which the re-entrant impulse uses the atrioventricular node as the anterograde limb of the circuit and the accessory pathway in the retrograde direction).

(4) Continuous and incremental high right atrial pacing was performed to determine the highest atrial cycle length which would support 1:1 anterograde conduction via the atrioventricular node. In patients with accessory pathways the test was repeated from a pacing site as close to the accessory pathway as possible to determine the highest rate at which it could conduct 1:1.

(5) The mechanism of reciprocating atrioventricular tachycardia was confirmed by endocardial mapping of ventriculoatrial conduction during the tachycardia.

(6) In those patients in whom reciprocating tachycardia could be initiated the zone over which atrial premature beats, both from the high right atrium and from an atrial site close to the accessory pathway, could initiate tachycardia was recorded (initiation zone). The cycle length of tachycardia and the conduction times of the components of the re-entry circuit were measured.

(7) Atrial fibrillation was induced by rapid atrial pacing in those patients in whom this arrhythmia was the presenting rhythm disturbance and in the one patient in whom no arrhythmia had previously been documented. During atrial fibrillation the ventricular response was assessed by recording the shortest and mean RR intervals.

The electrophysiological studies defined three groups of patients. Group 1 consisted of those patients with the Wolff-Parkinson-White syndrome in whom rapidly conducted atrial fibrillation (mean ventricular rate in excess of 250 a minute) was the major rhythm disturbance (Fig. 1). In addition, these patients had orthodromic reciprocating atrioventricular tachycardia. In two patients this arrhythmia degenerated spontaneously to atrial fibrillation (Fig. 2). There was sustained atrial fibrillation in three patients while in the other the first episode of atrial fibrillation terminated spontaneously while the second was sustained. Reciprocating atrioventricular tachycardia was induced by single atrial extrastimuli in three patients: in the other neither single nor double atria extrastimuli suceeded (case 1). In none of these patients was it possible to assess the highest rate of 1:1 conduction down the accessory pathway because of the development of atrial fibrillation. In one patient (case 3) atrioventricular nodal function suggested an accessory atrio-His pathway.[13]

Nine patients had reciprocating atrioventricular tachycardia alone (group 2); this was associated with an accessory atrioventricular pathway (Wolff-Parkinson-White syndrome) in seven while the remainder had intranodal re-entry. Only one patient had overt Wolff-Parkinson-White syndrome, the other six having concealed accessory pathways.[14]

Group 3 comprised those with paroxysmal atrial fibrillation or flutter unassociated with pre-excitation. The control studies demonstrated a prolonged corrected sinus node recovery time in one patient (case 16) though there was no history

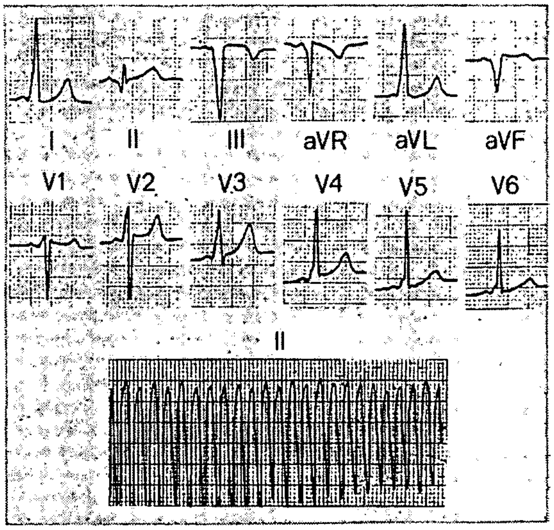

Fig. 1 *Case 1: electrocardiogram during sinus rhythm shows Wolff-Parkinson-White syndrome type A. Rhythm strip (lead II) shows atrial fibrillation: ventricular rate exceeds 400/min.*

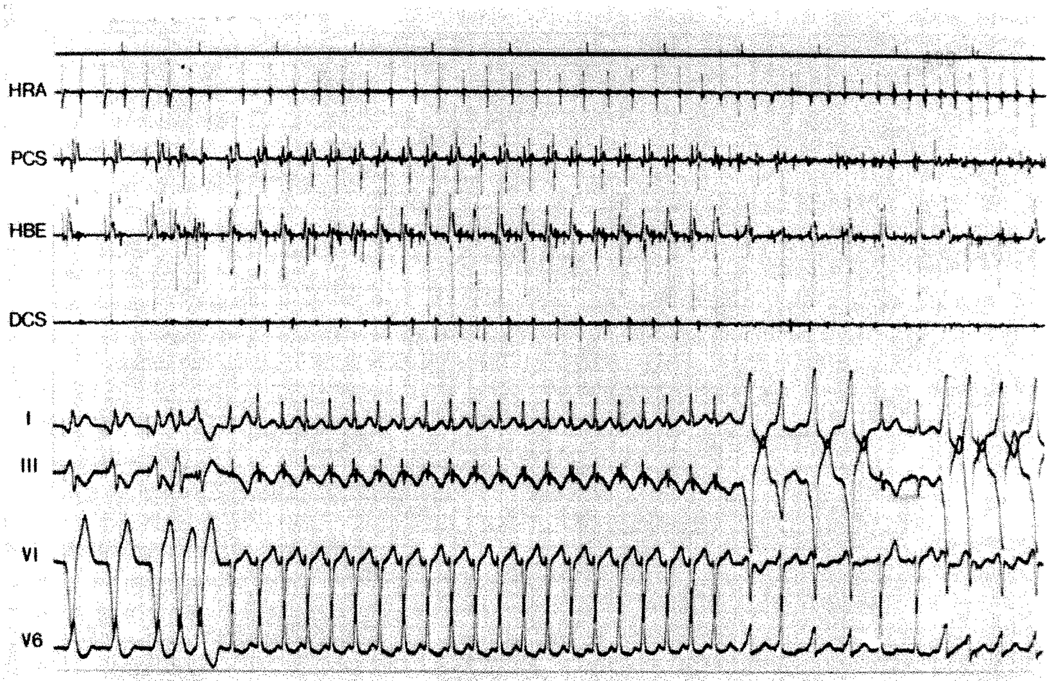

Fig. 2 *Case 1: intracardiac and surface electrocardiograms (paper speed 25 mm/s). HRA, high right atrial electrogram; PCS, proximal coronary sinus electrogram; HBE, His bundle electrogram; DCS, distal coronary sinus electrogram. During right ventricular pacing a critically-timed ventricular extrastimulus and a ventricular extrasystole (complexes 4 and 5) initiate re-entry atrioventricular tachycardia which leads to atrial fibrillation.*

or other evidence suggestive of sinuatrial disease.[15] One patient known to have paroxysmal atrial fibrillation and flutter developed persistent atrial flutter and was then started on amiodarone.

DRUG REGIMEN

Treatment with amiodarone was begun after suitable trials of appropriate conventional anti-arrhythmic drugs had failed (Table 1). The dose was 600 mg a day for the first month and 400 mg a day for the next month, with maintenance on 200 mg a day if the response was satisfactory.

THERAPEUTIC ASSESSMENT

The method of assessment of therapeutic benefit varied with the nature of the arrhythmia. In group 1 (Table 2) in whom rapidly conducted atrial fibrillation complicating the Wolff-Parkinson-White syndrome was the major rhythm disturbance, limited electrophysiological testing was performed. A single quadripolar electrode was used to stimulate and record from the high right atrium and then moved to a site as close as possible to the atrial insertion of the accessory pathway. From these two positions it was possible to measure corrected sinus node recovery times, atrial effective refractory period, and the highest 1:1 rate sustained by the accessory pathway in the anterograde direction. The ability to initiate re-entry tachycardia by single or multiple atrial premature stimuli was assessed (Table 3); where a single stimulus succeeded the initiation zone was measured. Atrial fibrillation was induced in all patients and the ventricular response assessed. In all four the study was performed three months after the start of treatment.

In the second group of patients (Table 3) re-assessment was performed by repeated 24-hour ambulatory electrocardiographic monitoring using Oxford Medilog recorders and a Reynolds Pathfinder analyser; six underwent limited electrophysiological investigation because they remained symptomatic: case 8 only developed recurrent arrhythmia during transient reduction to 200 mg a day.

Assessment of the third group was by ambulatory

Table 1 *Patients*

Case no.	*Age (y)*	*Diagnosis/arrhythmia*	*Previous treatment*	*Duration of follow-up (mth)*
1	26	WPW A + AF + RT	Q	17
2	58	WPW A + AF + RT	Di, Q	15
3	19	WPW A + AF + RT	Q, Pr	21
4	60	WPW A + AF + RT	Pr	8
5	56	Conc WPW A + RT	D, V, Q	3
6	63	Conc WPW A + RT	Q, V, O, D	23
7	40	Conc WPW A + RT	V, Di, D, O, Q	14
8	48	Conc WPW A + RT	V, D, Pc	21
9	60	IntraAV nodal RT	Di, V, O, Pr, Q, Po, Pc, D, S	14
10	45	IntraAV nodal RT	Po, Pi, Q, V	12
11	47	Conc WPW A + RT	Po, Pc, Q, D, V, Di	4
12	52	WPW A + RT	V, Q, D, Pc	12
13	34	Conc WPW A + RT	V, D, Q, Po	3
14	33	A Fl	D, Pr, Pc, O Q, V	3
15	53	AF/A Fl	D, Po	19
16	34	AF	Q, Di, D	22
17	52	AF	Di, Q, D	20
18	57	AF	D, Q	22
19	46	AF	D, Q	5
20	64	A Fl	D, Q	25
21	68	AF	Pc, Po, D, Q	12

WPW, Wolff-Parkinson-White syndrome; AF, atrial fibrillation; A Fl, atrial flutter; RT, re-entry tachycardia; Conc, concealed; Pr, procainamide; Po, propranolol; Pi, pindolol; Pc, practolol; D, digoxin; Di, disopyramide; V, verapamil; O, oxprenolol; Q, quinidine; S, sotalol.

monitoring without repeat electrophysiological study.

Ophthalmological examination was undertaken at three months to observe the corneal microdeposits known to be a marker of treatment with this drug.[8 16] Biochemical estimation of thyroid function was also performed to exclude hyperthyroidism[17] and hypothyroidism[18] known sometimes to be a complication of treatment.

Table 2 *Patients with WPW syndrome and atrial fibrillation before and after amiodarone*

Case no.	*CSNRT (ms)*	*Atrial fibrillation*		*AERP (ms)*	*Accessory pathway ERP (ms)*
		MRR (ms)	*SRR (ms)*		
1	170	208	165	190	⩽200
	290	375	230 (T)	260	290
2	340	240	190	250	280
	260	428	290 (T)	320	350
3	250	230	170	200	220
	200	360	220	260	⩽270
4	155	240	190	240	275
	310	410	280 (T)	320	340

CSNRT, corrected sinus node recovery time; MRR, mean RR interval during atrial fibrillation; SRR, shortest RR interval during atrial fibrillation; AERP, atrial effective refractory period; ERP, effective refractory period; T, spontaneous termination.

Table 3 *Patients with PRAVT before and after amiodarone*

Case no.	*CSNRT (ms)*	*AERP (ms)*	*CL PRAVT (ms)*	*Initiation zone from atrium (ms)*
1	170	190	310	—
	290	260	430 (T)	275–265
2	340	250	330	280–260
	260	320	470 (T)	350–330
3	250	200	265	220–210
	200	260	340	—
4	155	240	325	270–250
	310	320	420	335–325
5	80	200	325	270–250
	170	250	500	620–260
8	140	230	280	(2)
	120	250	500 (T)	(2)
9	420	190	410	280–240
	350	250	390	380–310
11	320	240	330	390–250
	340	300	475	380–310
12	240	220	315	310–230
	230	360	400	380–270
13	1150	230	455	400–240
	190	250	470	360–260

CSNRT, corrected sinus node recovery time; AERP, atrial effective refractory period; CL PRAVT, cycle length of paroxysmal reciprocating atrioventricular tachycardia; initiation zone, width of the zone over which single atrial extrastimuli initiate PRAVT: (2) = 2 atrial extrastimuli required; T, spontaneous termination.

Results

The findings of the limited electrophysiological study performed in group 1 three months after starting treatment are shown in Table 3. All showed an increase in the effective refractory period of the atrium but, more importantly, atrial fibrillation was more difficult to induce than during the control study, was conducted with a mean ventricular rate below 200 a minute, and was now well tolerated. Atrial fibrillation was only produced in the patients on amiodarone by rapid atrial pacing, whereas there had been spontaneous transformation from re-entry tachycardia in two patients during the control study.[19] Atrial fibrillation terminated spontaneously in three patients (Fig. 3) but only in one when not on treatment. The influence of the drug on the ability of atrial premature beats to initiate re-entry atrioventricular tachycardia was variable. In the patient (case 1) in whom neither

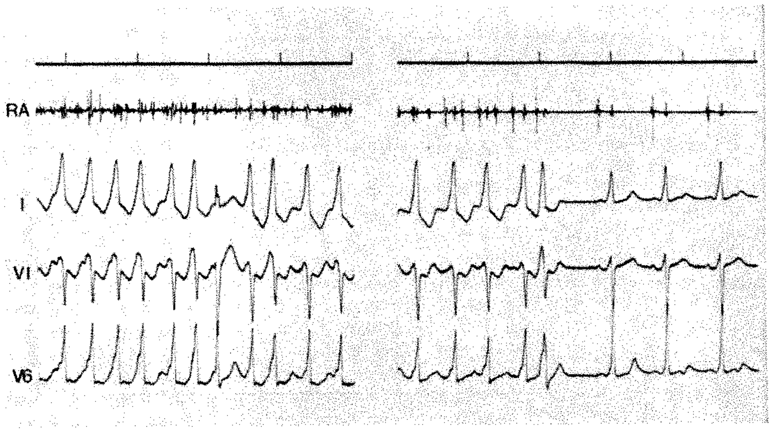

Fig. 3 *Case 1: after three months' treatment with amiodarone: a right atrial electrogram (RA) shown with leads I, V1, and V6 (paper speed 25 mm/s). During atrial fibrillation the ventricular rate is 165 a minute: the arrhythmia also terminates spontaneously.*

single nor double premature stimuli could initiate tachycardia in the first study it was possible to induce tachycardia from the atrium with single stimuli though over a narrow zone (10 ms). In two patients the zone remained similar in width but the coupling intervals were longer; in the fourth patient (case 3) the zone was abolished. The rate of sustained re-entry tachycardia was slower in all. In three patients re-entry tachycardia terminated spontaneously after a brief period (Fig. 4); this had never occurred during the control study. In two patients termination occurred in the anterograde direction while in the other it occurred in the retrograde pathway.

The results of treatment with amiodarone in group 2 are shown in Table 3. Four patients remained symptom-free on maintenance therapy, though one patient suffered a relapse of his tachycardia six weeks after his dose was decreased to 200 mg a day; he has been maintained on 400 mg a day without symptoms. Six patients had limited electrophysiological studies while on amiodarone and it was possible to initiate sustained re-entry tachycardia in all; this complemented the findings of ambulatory monitoring in the five patients who noticed no improvement. As in group 1, the tachycardia was slower and the initiation zone did not change consistently: it was wider in three and narrower in two. In the other patient two atrial extrastimuli were required to initiate tachycardia both during the control study and while on amiodarone. In one patient (case 13) in whom a

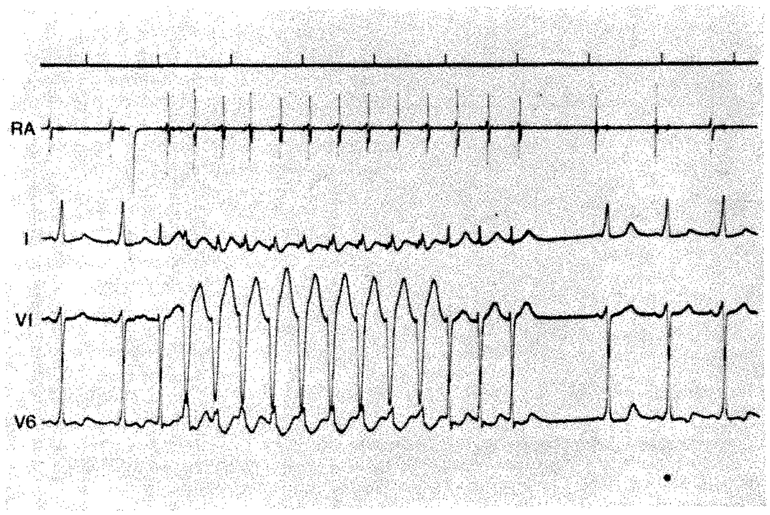

Fig. 4 *Case 1: recordings during re-entry atrioventricular tachycardia while on amiodarone, abbreviations as in Fig. 3. An atrial extrastimulus initiates tachycardia, at first complicated by left bundle-branch block. The tachycardia terminates spontaneously in the anterograde direction.*

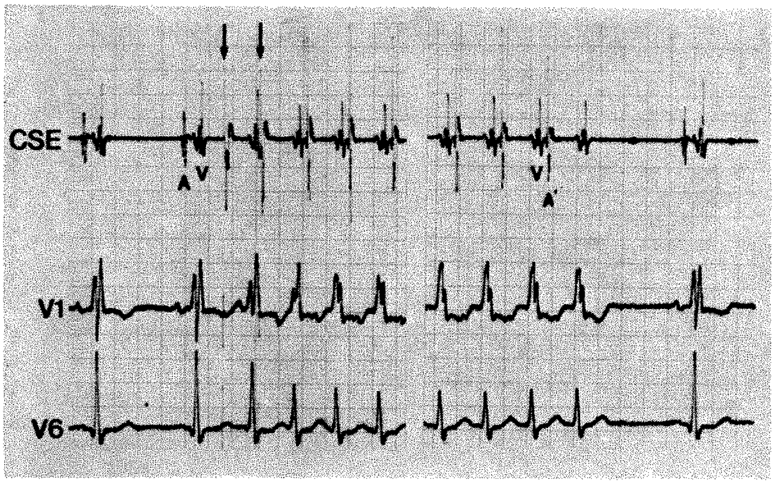

Fig. 5 *Case 8: simultaneous coronary sinus and surface electrocardiograms after treatment with amiodarone for three months. A, left atrial; V, left ventricular activation. The patient has right bundle-branch block and a concealed left-sided accessory pathway. Tachycardia is initiated by two atrial extrastimuli* (arrows): *note retrograde left atrial depolarisation (A'). After 30 s the tachycardia terminates spontaneously in the retrograde direction.*

more complete electrophysiological study was performed while on amiodarone the change in rate of the tachycardia was the result of lengthening of conduction time in both the atrioventricular node and the accessory pathway. The limited study on the patient who relapsed on the maintenance dose of amiodarone (case 8) showed that it was possible to initiate re-entry tachycardia but that each episode terminated with block in the retrograde limb of the circuit (Fig. 5). The results of ambulatory monitoring performed on the patients who became asymptomatic on amiodarone showed them to be virtually free of extrasystoles, while the symptomatic group continued to have extrasystoles which often initiated tachycardia (Fig. 6). Of the patients in groups 1 and 2 who had reciprocating atrioventricular tachycardia and were studied while on amiodarone there was no consistent difference in the electrophysiological changes between those who responded and those who did not.

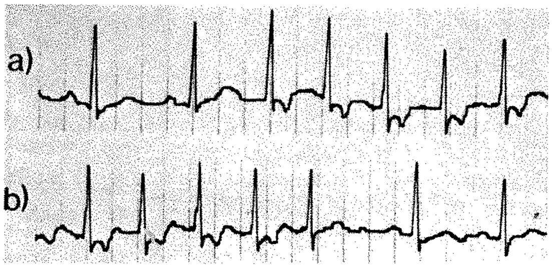

Fig. 6 *Case 5: ambulatory electrocardiograms (monitor lead) in a patient in whom re-entry atrioventricular tachycardia persisted while on amiodarone.* (a) *In sinus rhythm a supraventricular extrasystole initiates re-entry tachycardia;* (b) *tachycardia terminates spontaneously after two hours.*

All but one in group 3 were asymptomatic after three months of treatment, the failure occurring in a patient with atrial flutter. In the other patients ambulatory monitoring showed that, in keeping with the clinical features, there was no sustained arrhythmia: in particular, the two patients with prolonged sinus node recovery times showed neither bradycardia nor sinus arrest. The conspicuous action of amiodarone on atrial myocardium was demonstrated in the patient in whom atrial flutter became established (Fig. 7). In the control state the atrial rate was 330 a minute with 2:1 atrioventricular conduction (Fig. 7b). After two weeks of treatment with amiodarone the atrial rate had fallen to 220 and 2:1 block persisted (Fig. 7c). Two weeks later the atrial rate was even slower at 190 a minute, still showing a 2:1 atrioventricular response (Fig. 7d). Rapid right atrial pacing induced sinus rhythm (Fig. 7e) which has been maintained on continuous treatment (Fig. 7f).

SIDE EFFECTS

Corneal microdeposits were seen in all patients but in none was it necessary to discontinue the drug: there were no visual symptoms. The alterations in thyroid function tests reflected the interference of amiodarone with the metabolism of thyroid hormones[20 21]; all patients remained euthyroid.

Two patients stopped amiodarone because of other side effects, in both after several months of successful treatment. Case 6 had been free of arrhythmia for 23 months for the first time in 36 years when he developed photodermatitis[22]; when treatment was stopped, tachycardia recurred and

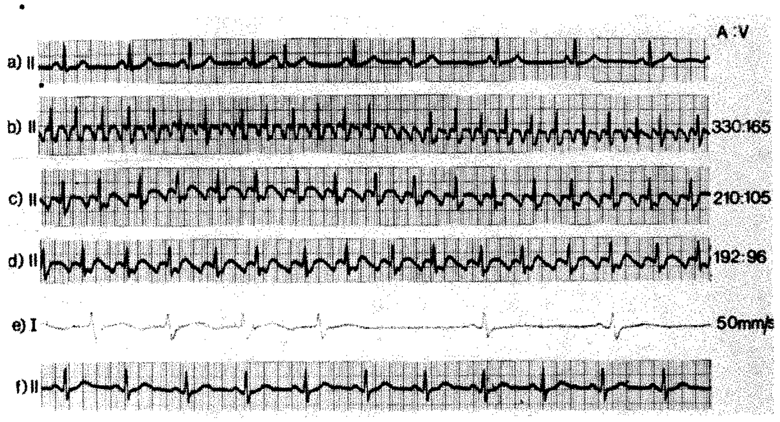

Fig. 7 *Case 15: electrocardiograms (lead II, 25 mm/s, except* (c)*; lead I, 50 mm/s) in a patient with chronic atrial flutter. To the right the atrial (A) and ventricular (V) rates are indicated:* (a) *sinus rhythm (with one atrial extrasystole) six months before onset of atrial flutter;* (b) *atrial flutter with 2:1 atrioventricular block, transiently increased in the middle of the tracing by carotid sinus massage;* (c) *after amiodarone (two weeks): the atrial rate has fallen to 210 a minute; 2:1 atrioventricular block persists;* (d) *after four weeks' treatment the atrial rate has decreased further;* (e) *rapid atrial pacing while on amiodarone terminates the arrhythmia; sinus rhythm ensues;* (f) *three months after conversion to sinus rhythm, on maintenance amiodarone.*

the dermatitis gradually improved. In case 19 in whom paroxysmal atrial fibrillation occurred two to six times a week he had no attacks for four months while on amiodarone. He stopped treatment, however, because of persistent insomnia, restlessness, and nightmares; subsequently arrhythmias have recurred though less frequently. In other patients difficulty in sleeping, unpleasant dreams, a bitter taste in the mouth, and restlessness have been noted, but in none were the symptoms severe enough to warrant discontinuing treatment.

Discussion

Amiodarone was introduced for the treatment of coronary artery disease because it was shown to cause coronary vasodilatation and to reduce the heart rate and thereby decrease myocardial oxygen consumption.[9] At the cellular level there is no apparent membrane stabilising effect when it is given orally and its antiarrhythmic action appears to result from prolongation of the duration of the action potential of myocardial cells.[23] No effect has been seen on resting membrane potential or action potential amplitude and there is only minimal change in the maximum rate of rise of the action potential.[24] Precisely how these effects are achieved is uncertain though non-competitive antagonism of both alpha- and beta-adrenergic activity,[25] and attenuation of the effects of glucagon on the heart[26] have been described. Though the clinical action of the drug in man mimics the effects of hypothyroidism and it is an iodinated compound, there is no evidence that it interferes with the cardiac effects of thyoid hormones.[20]

Electrophysiological studies in man have disclosed that amiodarone increases the refractory periods of atrial and ventricular myocardium, prolongs conduction time in the atrium, and lengthens the refractory period of the atrioventricular node and accessory pathways.[7 26 27] In clinical studies it has been shown to be effective against a wide variety of ventricular and supraventricular arrhythmias, particularly reciprocating atrioventricular tachycardia associated with the Wolff-Parkinson-White syndrome.[5 8] Wellens *et al.*[7] were able to initiate tachycardia on repeat electrophysiological testing in 10 of their 15 patients: the possibility that this was because their second study was too soon (two weeks) after the start of treatment[28] is not applicable to our patients who were tested three months after the start of treatment. This latter study[28] was performed 26 to 85 days after the start of treatment and re-entry tachycardia could not be initiated in any of the four patients retested.

The limited pharmacodynamic information suggests that amiodarone is somewhat variably absorbed resulting in low blood levels because of strong tissue-binding and long half-life of about 28 days.[10]

In this study 21 patients were treated with the same reducing regimen of oral amiodarone. Restrictions on its use in Great Britain allow it to be tried only after conventional treatment has failed. Fifteen became asymptomatic during the first month of treatment and all but one could be maintained on 200 mg a day.

In group 1 various combinations of conventional antiarrhythmic drugs including disopyramide, quinidine, and procainamide had failed to control the symptoms or reduce the ventricular rate appreciably during atrial fibrillation. The atrial stabilising property of amiodarone was reflected in a greater resistance to the induction of atrial fibrillation, and in its spontaneous termination. The depressant action of the drug on anterograde conduction via the accessory pathway protected against the profound haemodynamic effects of atrial fibrillation in these patients.

Drugs that prevent re-entry atrioventricular tachycardia may do so by abolishing initiating extrasystoles or modifying circuit behaviour, as well as other less common factors. Modifications of circuit behaviour include abolishing the initiation zone as well as depressing conduction in either atrioventricular pathway so that any tachycardia is terminated promptly. In this series clinical benefit seemed more closely related to spontaneous termination of induced tachycardia than to changes in initiation zone from the atria. The method of termination was either by block in the retrograde direction, presumably the accessory pathway, or in the anterograde direction. While anterograde block may occur in either the atrioventricular node or His-Purkinje system, its occurrence in one patient when he was supine, but not when he was upright, suggested termination in the atrioventricular node.[29] We have examined only one method of initiation of re-entry tachycardia, albeit the most common, and it may be that other effects on the mechanism of induction of tachycardia played a part. Paradoxical aggravation of the tendency to tachycardia sometimes seen with drugs[30] did not occur in any patient.

Twenty-four-hour monitoring corroborated the clinical impression of therapeutic benefit. In those patients who failed to respond, supraventricular extrasystoles persisted, often followed by paroxysms of re-entry tachycardia, while in the asymptomatic group the absence of extrasystoles was striking.

In the patients with atrial fibrillation and flutter, the absence of arrhythmias during 24-hour electrocardiographic monitoring correlated well with clinical improvement. No patient had asystolic pauses or periods suggesting sinuatrial block. While the clinical importance of any action of amiodarone on the sinus node remains unresolved[31 32] none of our patients had prolonged sinus node recovery times after amiodarone.

The regimen in these patients is similar to that used by other investigators[8]; available evidence suggests that a steady state is achieved using a single daily dose though there is no information at present on the range of blood levels achieved. While variability in the metabolism and excretion of the drug may well explain the differences in clinical efficacy, those who failed to benefit did so at the maximum dose. The selection of patients by virtue of their failure to respond to conventional antiarrhythmic agents may partly explain our lower success rate than that of others.[5]

Amiodarone appears to act widely on the conducting system and myocardium and may, therefore, be particularly effective in complex arrhythmias, including some cases of paroxysmal re-entry atrioventricular tachycardia. We have found it especially effective in atrial fibrillation, and where this is associated with a rapid ventricular rate because of the Wolff-Parkinson-White syndrome amiodarone may obviate surgical treatment. The incidence of side effects remains small but because experience is still somewhat limited close observation is recommended. Further pharmacodynamic studies are required to determine the absorption and metabolism of the drug and to ensure that it is used safely and effectively in suitable patients.

References

1 Gallagher JJ, Gilbert M, Svenson RH, Sealy WC, Kasell J, Wallace AG. Wolff-Parkinson-White syndrome. The problem, evaluation and surgical treatment. *Circulation* 1975; **51**: 767–85.

2 Vastesaeger M, Guillot P, Rasson G. Etude clinique d'une nouvelle médication antiangoreuse. *Acta Cardiol (Brux)* 1967; **22**: 483–500.

3 Van Schepdael J, Solvay H. Etude clinique de de l'amiodarone dans les troubles du rythme cardiaque. *Presse Med* 1970; **78**: 1849–50.

4 Coumel Ph, Bouvrain Y. Etude clinique des effets pharmacodynamiques et antiarythmiques de l'amiodarone. *J Agrégés* 1973; **6**: 69–81.

5 Rosenbaum MB, Chiale PA, Halpern MS, *et al.* Clinical efficacy of amiodarone as an antiarrhythmic agent. *Am J Cardiol* 1976; **38**: 934–44.

6 Rosenbaum MB, Chiale PA, Ryba D, Elizari MV. Control of tachyarrhythmias associated with Wolff-Parkinson-White syndrome by amiodarone hydrochloride. *Am J Cardiol* 1974; **34**: 215–23.

7 Wellens HJJ, Lie KI, Bär FW, *et al.* Effect of amiodarone in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1976; **38**: 189–94.

8 Wheeler PJ, Puritz R, Ingram DV, Chamberlain DA. Amiodarone in the treatment of refractory supraventricular and ventricular arrhythmias. *Postgrad Med J* 1979; **55**: 1–9.

9 Charlier R, Deltour G, Baudine A, Chaillet F. Pharmacology of amiodarone, an anti-anginal drug with a new biological profile. *Arzneim Forsch* 1968; **11:** 1408–17.

10 Broekhuysen J, Laruel R, Sion R. Recherches dans la serie des benzofurannes. XXXVII. Etude comparée du transit et du métabolisme de l'amiodarone chez diverses espèces animales et chez l'homme. *Arch Int Pharmacodyn Ther* 1969; **177:** 340–59.

11 Curry PVL. Fundamentals of arrhythmias: modern methods of investigation in cardiac arrhythmias. In: Krikler DM, Goodwin JF, eds. *Cardiac arrhythmias: the modern electrophysiological approach.* London, Philadelphia, Toronto: WB Saunders, 1975: 39–80.

12 Narula OS, Samet P, Javier R. Significance of the sinus node recovery time. *Circulation* 1972; **45:** 140–58.

13 Gallagher JJ, Sealy WC, Kasell J, Wallace AG. Multiple accessory pathways in patients with the pre-excitation syndrome. *Circulation* 1976; **54:** 571–91.

14 Krikler DM, Rowland E. Concealed pre-excitation. *J Electrocardiol* 1978; **11:** 209–11.

15 Evans TR, Callowhill EA, Krikler DM. Clinical value of tests of sino-atrial function. *Pace* 1978; **1:** 2–7.

16 Francois J. Cornea verticillata. *Bull Soc Belge Ophtalmol* 1968; no. 150: 656–70.

17 Jonckheer MH, Blockx P, Kaivers R, Wyffels G. Hyperthyroidism as a possible complication of the treatment of ischemic heart disease with amiodarone. *Acta Cardiol (Brux)* 1973; **28:** 192–200.

18 Massin JP, Thomopoulos P, Karam J, Savoie JC. Le risque thyroidien d'un nouveau coronarodilatateur iodé: l'amiodarone (Cordarone). *Ann Endocrinol (Paris)* 1971; **32:** 438–48.

19 Campbell RWF, Smith RA, Gallagher JJ, Pritchett ELC, Wallace AG. Atrial fibrillation in the pre-excitation syndrome. *Am J Cardiol* 1977; **40:** 514–20.

20 Pritchard DA, Singh BN, Hurley PJ. Effects of amiodarone on thyroid function in patients with ischaemic heart disease. *Br Heart J* 1975; **37:** 856–60.

21 Rees LH, Ward DE, Camm AJ, Al-Handi A. Effect of amiodarone on thyroid function. Amiodarone in cardiac arrhythmias. *Royal Society of Medicine International Congress and Symposium Series no. 16* 1979: 53–6.

22 Geerts ML. Amiodarone pigmentation. An electron microscopic study. *Arch Belg Dermatol Syph* 1971; **27:** 339–51.

23 Singh BN, Vaughan-Williams EM. The effect of amiodarone, a new antianginal drug, on cardiac muscle. *Br J Pharmacol* 1970; **39:** 657–67.

24 Facquet J, Nivet M, Grosgogeat Y, Alhomme P, Vachon J. L'influence de l'amiodarone sur le rythme cardiaque et l'électrocardiogramme. *Therapie* 1970; **25:** 335–41.

25 Charlier R. Cardiac actions in the dog of a new antagonist of adrenergic excitation which does not produce competitive blockade of adrenoceptors. *Br J Pharmacol* 1970; **39:** 668–74.

26 Polster P, Broekhuysen J. The adrenergic antagonism of amiodarone. *Biochem Pharmacol* 1976; **25:** 131–4.

27 Olsson SB, Brorson L, Varnauskas E. Class 3 antiarrhythmic action in man. Observations from monophasic action potential recordings and amiodarone treatment. *Br Heart J* 1973; **35:** 1255–9.

28 Rasmussen V, Berring J. Effect of amiodarone in the Wolff-Parkinson-White syndrome. *Acta Med Scand* 1979; **205:** 31–7.

29 Curry PVL, Rowland E, Fox KM, Krikler DM. The relationship between posture, blood pressure and electrophysiological properties in patients with paroxysmal supraventricular tachycardia. *Arch Mal Coeur* 1978; **71:** 293–9.

30 Krikler DM, Curry PVL, Attuel P, Coumel Ph. "Incessant" tachycardias in Wolff-Parkinson-White syndrome. I: Initiation without antecedent extrasystoles or PR lengthening, with reference to reciprocation after shortening of cycle length. *Br Heart J* 1976; **38:** 885–96.

31 Brown AK, Primhak RA, Newton P. Use of amiodarone in bradycardia-tachycardia syndrome. *Br Heart J* 1978; **40:** 1149–52.

32 Touboul P, Atallah G, Gressard A, Kirkorian G. Effect of amiodarone on the sinus node in man. *Br Heart J* 1979; **42:** 573–8.

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Clinical antiarrhythmic effects of amiodarone in patients with resistant paroxysmal tachycardias

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SUMMARY Oral amiodarone, an iodine-containing antiarrhythmic agent, was administered to 72 patients with recurrent paroxysmal tachycardias. Thirty-nine patients had tachycardias associated with the Wolff-Parkinson-White syndrome, 15 patients had paroxysmal atrial fibrillation unassociated with the Wolff-Parkinson-White syndrome, and 18 patients had ventricular tachycardia. In all patients, the frequency of symptomatic attacks had not been reduced by at least three other antiarrhythmic agents alone or in combination. The response to amiodarone treatment was graded according to the patients' subjective response (total suppression, partial suppression, and no effect). Overall, 57 per cent of patients had total abolition of attacks and another 22 per cent had a partial suppression of attacks. Side effects, the most common of which were photosensitivity and gastrointestinal upsets, occurred in 44 per cent and were sufficiently severe to warrant withdrawal of treatment in 15 per cent. These results confirm that amiodarone is of considerable value in the treatment of recurrent paroxysmal arrhythmias resistant to other drugs.

Amiodarone, a benzfuran derivative, is an antiarrhythmic drug which was originally used in Europe as an antianginal agent.[1] Singh and Vaughan-Williams[2] subsequently demonstrated that the drug prolonged the action potential. Intracardiac electrophysiological studies in man indicated that oral amiodarone increased the refractoriness of atrial myocardium, atrioventricular node, ventricular myocardium, and anomalous bypass tracts.[3] Recent clinical studies[4–7] have shown the beneficial effect of the drug in a variety of arrhythmias, the majority of which were refractory to several other antiarrhythmic agents. These studies indicate that amiodarone is an extremely effective antiarrhythmic agent and forms an important addition to the therapeutic armamentarium. As yet, in this country, the drug has no clinical trials certificate and can only be prescribed for specified named patients.

We report our experience of the use of oral amiodarone in 39 patients with tachyarrhythmias associated with the Wolff-Parkinson-White (WPW) syndrome, 15 patients with paroxysmal atrial fibrillation or flutter unassociated with the WPW syndrome, and 18 patients with recurrent paroxysmal ventricular tachycardia.

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Patients and methods

The patients, aged 12 to 73 years, had distressing paroxysmal palpitation repeatedly documented electrocardiographically, which had not been symptomatically improved by any other antiarrhythmic drugs. All patients had previously been treated with at least three other antiarrhythmic drugs in conventional doses. The details of the patients and their arrhythmias are summarised in Table 1. Electrophysiological studies were performed in all patients with accessory pathways to define the tachycardia mechanism and the characteristics of the accessory pathway. Recurrent paroxysmal atrial fibrillation or flutter and ventricular tachycardia were diagnosed from 24-hour ambulatory recordings or from 12 lead electrocardiograms taken during the attack. Patients with ventricular tachycardia were subdivided on the basis of the coronary arteriographic and left ventricular angiographic findings.

Oral amiodarone was started using a loading dose of 600 mg daily for one week, 400 mg daily for one week, and a subsequent dosage of at least 200 mg daily adjusted according to the response. Amiodarone was not continued for more than four weeks if there was no therapeutic response.

Table 1 *Results*

Response	*Total*	*Partial*	*Nil*	*Total (n)*
*Wolff-Parkinson-White (39 patients)**				
Paroxysmal atrial fibrillation	4	1	1	6
Paroxysmal atrial fibrillation/supraventricular tachycardia	7	1	2	10
Supraventricular tachycardia	12	7	4	23
Total	23	9	7	39
Paroxysmal atrial flutter or fibrillation (15 patients)†				
Fibrillation	6	3	2	11
Flutter	2	1	1	4
Total	8	4	3	15
Ventricular tachycardia (18 patients)‡				
Ischaemic	8	1	3	12
(Acute myocardial infarction)	(3	1	—	4)
Cardiomyopathy	1	2	1	4
Unknown cause	1	—	1	2
Total	10	3	5	18

* Type A = 25, Type B = 3, Concealed = 11, male $n = 20$, female $n = 19$.
† Male, 10; female, 5. ‡ Male $n = 13$, female $n = 5$.

Intermittent 24-hour ambulatory monitoring is not a practical method of assessment in patients with relatively infrequent arrhythmias occurring over a long period of time. For this reason we chose to grade the response to treatment according to the frequency of subjective symptoms rather than objective ambulatory electrocardiographic findings which, because of the intermittent nature of arrhythmias, are often difficult to interpret. In addition, only patients with sustained symptomatic paroxysms of tachycardia were selected. Patients with ectopic beats only were excluded because these arrhythmias are more difficult to relate to symptoms.

The response to treatment was therefore graded into three categories according to the patient's subjective assessment: total suppression of attacks: no awareness of further attacks; partial suppression: patient aware of less frequent and less troublesome attacks; no demonstrable effect: the patient reported no improvement. These criteria are similar to those of Rosenbaum *et al.*[6]

Follow-up has ranged from three months to five years. Thyroid function tests, liver function tests, full blood count, electrolytes, and urea were performed at regular intervals during follow-up. The presence or absence of corneal deposits[8] and other unwanted effects were noted at each visit.

Results

The overall results in each category of arrhythmia are shown in Table 1.

(a) WOLFF-PARKINSON-WHITE TACHYCARDIAS

Of the 39 patients with symptomatic tachycardias associated with the WPW syndrome, all of whom had failed to respond to disopyramide, quinidine, beta blockers, or verapamil, 23 (59%) had total abolition of attacks. The majority of these patients were suffering from atrioventricular re-entrant tachycardia. The maintenance dose in 17 of these 23 patients was 200 mg daily and only one patient required more than 600 mg daily (Table 2). Nine patients had partial suppression and seven patients failed to notice any symptomatic improvement despite higher maintenance doses.

(b) PAROXYSMAL ATRIAL FIBRILLATION OR FLUTTER UNASSOCIATED WITH WPW SYNDROME

All the patients in this group had been unsuccessfully treated with disopyramide, quinidine, digoxin, verapamil, or beta blockers. Of the total of 15 patients, total suppression was achieved in eight patients, two of whom had paroxysmal atrial flutter. In six of these eight patients the maintenance dose of 200 mg daily was sufficient to control the arrhythmia and none required more than 400 mg daily. None of these patients had evidence of coronary artery disease or any other disorder which may have predisposed to the development of atrial fibrillation. There was no evidence of sinus node dysfunction before amiodarone treatment in any patient in this group.

(c) VENTRICULAR TACHYCARDIA

In 12 patients there was evidence of coronary artery disease (previous myocardial infarction in nine patients) confirmed by coronary arteriography. Six patients had abnormal left ventricular angiograms with evidence of aneurysm formation in four patients. Six patients had normal coronary arteries

Table 2 *Therapeutic effect versus maintenance dose*

Response *Dose (mg/day)*	*200*	*400*	*600*	*> 600*	*Total*
Wolff-Parkinson-White (39 patients)					
Total	17	3	2	1	23
Partial	4	3	2	—	9
Nil	1	3	2	1	7
Paroxysmal atrial fibrillation (15 patients)					
Total	6	2	—	—	8
Partial	3	—	1	—	4
Nil	1	1	1	—	3
Ventricular tachycardia (18 patients)					
Total	5	2	2	1	10
Partial	1	2	—	—	3
Nil	—	2	2	1	5

and four of these were considered to have a cardiomyopathy. In two patients the underlying aetiology of tachycardia was unknown. No patient had ventricular fibrillation. All patients were resistant to other antiarrhythmic agents which included the class I drugs disopyramide, mexiletine, and phenytoin.[9] Eight patients also had beta blocking agents without benefit. Four patients were started on amiodarone in the immediate post-infarction period after they had failed to respond to lignocaine and disopyramide. An excellent response was observed in three of these patients. Overall, total suppression was obtained in 10 of the 18 patients.

There appeared to be no apparent distinguishing characteristics of those in whom total suppression was achieved. For example, age, sex, location of accessory pathway in patients with the WPW syndrome, type of arrhythmia, or aetiology of ventricular tachycardia did not seem to influence the response to treatment. The duration of onset of action ranged from two days to three weeks. Of the poor responders with the WPW syndrome, four subsequently underwent cryosurgical ablation of the accessory pathway. Surgical treatment was also undertaken in two patients with the WPW syndrome who were intolerant to the drug despite an excellent response. This was also the case in two patients with partial suppression of paroxysmal atrial fibrillation, who, together with two others with no response, underwent surgical His bundle ablation. One patient with ventricular tachycardia of unknown aetiology eventually required surgical ablation of the abnormal focus, after failure to respond to amiodarone. Side effects other than corneal deposits occurred in 44 per cent of patients and included gastrointestinal upsets (14%), photosensitivity (17%), nightmares and vivid dreams (10%), headaches (7%), paraesthesiae (6%), epistaxis in one patient, and profound sinus bradycardia in two patients. Side effects necessitated discontinuation of treatment in 11 patients (gastrointestinal upset, four patients; nightmares, three patients; headaches, two patients; photosensitivity, two patients). The two patients with sinus bradycardia (WPW, one patient, atrial flutter, one patient) were treated by permanent pacing. Corneal deposits were observed in 51 patients at three months and in 43 of the 46 patients still on treatment at six months. In no patient did these deposits interfere with vision.

Most patients showed increases in T4 and free thyroxine index with normal thyroid hormone uptake tests but none developed clinical thyroid disease; these results are reviewed in detail elsewhere.[10] There appeared to be no relation between biochemical disturbance of thyroid function and antiarrhythmic efficacy. Abnormal liver function was noted in one patient who was subsequently found to have coincidental liver disease. No abnormalities of renal function or full blood count were observed.

Discussion

The major cellular electrophysiological effect of amiodarone is pronounced prolongation of action potential duration[2] with little effect on the rate of rise of the upstroke. In this respect it differs from other antiarrhythmic agents with the exception of sotalol.[11] Previously reported clinical studies[4–7] had shown the drug to be extremely effective in controlling a wide variety of recurrent tachyarrhythmias.

Rosenbaum *et al.*[5] noted total suppression in all 27 patients with tachyarrhythmias related to the WPW syndrome. This compares with 59 per cent of the current series though another 23 per cent had a good response. This difference may be accounted for by the fact that not all the patients reported by Rosenbaum *et al.*[5] had had previous treatment with three or more antiarrhythmic agents and may have been less resistant to medical treatment than our patients. The maintenance dose of amiodarone required to obtain total suppression, however, was greater than 300 mg daily in nine of 11 patients in Rosenbaum *et al.'s* initial series,[4] whereas only six of our 23 patients with total suppression required more than 200 mg daily. Differences in patient selection may also have contributed to the discrepancy between our results in this group and those of Rosenbaum *et al.*[5] If only the patients with paroxysmal atrial fibrillation associated with the WPW syndrome are considered, the success rate in terms of total abolition of attacks was 69 per cent. It is unlikely that the presence of this arrhythmia made any difference to the observed response. The proportion of patients with paroxysmal atrial fibrillation in our series is comparable to that of Rosenbaum's series.

Total suppression of attacks was obtained in a smaller porportion of patients (53%) with paroxysmal atrial fibrillation or flutter unassociated with the presence of an accessory pathway. This compares with 96 per cent of a series of 30 patients reported by Rosenbaum[5] which included seven patients with the WPW syndrome. Almost all of the remainder of these patients, however, had associated cardiovascular or pulmonary disease in contrast to our patients who were otherwise apparently healthy. In particular, no patient had evidence of sinus node disease on 24-hour ambulatory recordings, though one patient developed profound sinus bradycardia while on amiodarone which is known to depress sinus automaticity.[2 12] This side effect also occurred in one patient with the WPW syndrome and both patients were successfully treated by implantation of a permanent pacemaker.

The success of amiodarone in suppressing recurrent ventricular arrhythmias has been documented previously[5-7] in patients with ischaemic heart disease and in those with cardiomyopathy. Of Rosenbaum's series of 44 patients including 13 with evidence of coronary artery disease, total suppression of attacks was achieved in 34 (77%). Of our 12 patients with ischaemic heart disease, eight exhibited total suppression, including three patients with arrhythmias in the acute post-myocardial infarction period. Indeed, previous experience, though limited,[5 6] suggests that the drug is no less effective in the suppression of ventricular arrhythmias related to acute ischaemia. This beneficial effect is probably related to several actions of amiodarone. In experimental animals the drug has been shown to produce coronary vasodilatation,[13 14] to increase coronary flow,[14] to decrease left ventricular work, and to decrease left ventricular oxygen consumption.[13 14] These effects, by tending to relieve ischaemia, would be expected to have a beneficial effect on ventricular tachycardias related to ischaemia.

Amiodarone, however, also has several direct effects. For example, the intravenous administration of the drug to experimental animals has an acutely protective effect against the development of ventricular arrhythmias induced by ouabain,[2] aconitine crystals,[15] and coronary artery ligation.[5 15] It is not known whether these effects are related to the cellular actions of the drug. Chronic oral administration has also been shown to be effective in suppressing ventricular arrhythmias induced by coronary ligation[5] and under these circumstances the cellular effects of amiodarone, which are known to be pronounced after chronic administration,[2 5] may be of some importance. In man, chronic amiodarone administration increases the ventricular effective refractory period.[3] The relevance of this observation to the therapeutic effect of the drug is, however, unknown. In addition, there is no evidence to suggest that the effectiveness of amiodarone in atrial arrhythmias is simply related to prolongation of the atrial effective refractory period. On the other hand, prolongation of accessory pathway refractoriness is likely to be an important effect in the suppression of sustained atrioventricular re-entrant tachycardia associated with the WPW syndrome[3] but it cannot be assumed that this is the only factor involved. It is probable that the antiarrhythmic action of amiodarone is a result of the complex interaction of several effects, including suppression of ectopic impulses which may initiate tachycardia.[16 17] The relation of amiodarone-induced disturbances of thyroid function to observed clinical antiarrhythmic effects is not known. Singh and Vaughan-Williams[2] showed that the cellular effects of chronic amiodarone administration could be countered by simultaneous treatment with thyroxine. The precise mechanism of the biochemical disturbance is ill understood, however, and we have as yet not noted any relation between such disturbances and the antiarrhythmic efficacy of the drug. In any case it is unlikely that a "thyroid" effect could explain the rapid onset of action of the drug in a proportion of cases.

The incidence of side effects in our series is relatively high when compared with Rosenbaum's series,[5] though the commonest unwanted effects (gastrointestinal upset and photosensitivity) occurred in roughly the same proportion of patients in each study. The incidence of side effects necessitating withdrawal of amiodarone was much higher than that reported by Rosenbaum.[5] The reasons for this discrepancy are not clear, but do not appear to be related to the average maintenance dose or duration of treatment which are comparable in the two series. Corneal deposits were asymptomatic in all patients in whom they occurred, and we believe that this effect, which is reversible,[8] is not as serious as other authors have suggested.[5 6]

Although we agree with the principle of Rosenbaum's contention that the need for surgery is considerably diminished by the availability of amiodarone it is evident that in a small number of patients refractory to the drug surgical intervention has an important role.

In total, a beneficial therapeutic response was obtained in 79 per cent of patients. These results, though not as good as those obtained by some investigators,[4 5] clearly confirm early results[18] suggesting that amiodarone is of great value in the suppression of a variety of paroxysmal arrhythmias resistant to other antiarrhythmic drugs. The relatively high incidence of side effects is disappointing, however, and may limit the overall usefulness of the drug.

References

1 Vastesaeger M, Gillet P, Rasson G. Étude clinique d'une nouvelle medication antiangoreuse. *Acta Cardiol (Brux)* 1967; **22:** 483–500.
2 Singh BN, Vaughan-Williams EM. The effect of amiodarone, a new anti-anginal drug, on cardiac muscle. *Br J Pharmacol* 1970; **39:** 657–67.
3 Wellens HJJ, Lie KI, Bär FW, *et al.* Effect of amio-

darone in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1976; **38:** 189–94.

4 Rosenbaum M, Chiale PA, Ryba D, Elizari MV. Control of tachyarrhythmias associated with Wolff-Parkinson-White syndrome by amiodarone hydrochloride. *Am J Cardiol* 1974; **34:** 215–23.

5 Rosenbaum M, Chiale PA, Halpern MS, *et al.* Clinical efficacy of amiodarone as an antiarrhythmic agent. *Am J Cardiol* 1976; **38:** 934–44.

6 Leak D, Eydt JN. Control of refractory cardiac arrhythmias with amiodarone. *Arch Intern Med* 1979; **139:** 425–8.

7 Wheeler PJ, Puritz R, Ingram DV, Chamberlain DA. Amiodarone in the treatment of refractory supraventricular and ventricular arrhythmias. *Postgrad Med J* 1979; **55:** 1–9.

8 Vérin PH, Gendre PH, Barchewitz G, Laurent-Bronchat G, Yacoub M, Morax S. Thesaurismose cornéenne par l'amiodarone. Données récentes. *Arch Ophtalmol (Paris)* 1971; **31:** 581–96.

9 Vaughan-Williams EM. Classification of antidysrhythmic drugs. *Pharmacol Ther Bull* 1975; **1:** 115–38.

10 Rees L, Ward DE, Al-Hamdi A, Camm AJ. Effect of amiodarone on thyroid function. International congress and symposium series. no. 16. London: Royal Society of Medicine, 1980; 53–6.

11 Singh BN, Vaughan-Williams EM. A third class of antiarrhythmic action. Effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle, of MJ1999 and AH3474. *Br J Pharmacol* 1970; **39:** 675–87.

12 Touboul P, Porte J, Huerta F, Delahaye JP. Electrophysiological effects of amiodarone in man (abstract). *Am J Cardiol* 1975; **35:** 173.

13 Charlier R, Deltour G, Baudine A, Chaillet F. Pharmacology of amiodarone, an anti-anginal drug with a new biological profile. *Arzneim Forsch* 1968; **11:** 1408–17.

14 Petta JM, Zaccheo VJ. Comparative profile of L3428 and other antianginal agents on cardiac hemodynamics. *J Pharmacol Exp Ther* 1971; **176:** 328–38.

15 Charlier R, Deltour G. Correction des arythmies expérimentales par l'amiodarone. *J Pharmacol (Paris)* 1970; **1:** 175–82.

16 Tadei A, Richard M, Victor J, Delhumeau A, Geslin P. Étude de l'amiodarone dans les troubles du rythme ventriculaire. *Arch Med Ouest* 1974; **6:** 415–34.

17 Van Schepdael J, Solvay H. Étude clinique de l'amiodarone dans les troubles du rythme cardiaque. *Presse Med* 1970; **78:** 1849–50.

18 Coumel P, Bouvrain Y. Étude clinique des effets pharmacodynamiques et antiarythmiques de l'amiodarone. *J Agrégés* 1973; **6:** 69–81.

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Multicentre post-infarction trial of propranolol in 49 hospitals in the United Kingdom, Italy, and Yugoslavia

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SUMMARY A multicentre study of survivors of an anterior myocardial infarction is reported. The trial consisted of 720 patients and was a double-blind, placebo-controlled study with propranolol 40 mg three times a day. Trial entry was at two to 14 days (mean 8·5 days) and follow-up at one, three, and in most centres, six and nine months. The trial was designed to detect a 50 per cent reduction in mortality and this was not shown. The non-fatal reinfarction rate was similar in both groups. Subgroup analysis identified several prognostic risk factors for death, none of which interacted with treatment.

There have been 15 studies with four beta-adrenergic blocking drugs (propranolol, practolol, alprenolol, and oxprenolol) after acute myocardial infarction.[1–15] In 11 of these studies,[1–9 14 15] the drugs were started within the first 24 to 48 hours. Only in the first study with propranolol[1] was a reduction in mortality claimed. In another early intervention trial an important subgroup with an initial high heart rate also had a reduced mortality with practolol.[14] In the other four studies,[10–13] treatment was started two weeks or more after recovery from the acute attack and was continued for up to three years. Three of these trials yielded significant reductions in mortality with practolol[13] and alprenolol.[11 12] The present studies were undertaken to see whether propranolol gave comparable results with those of practolol[13] in patients with anterior infarction.

Patients and methods

From a total of 49 hospitals, 720 patients (609 men, 111 women) aged 70 or less entered a double-blind placebo-controlled study at two to 14 days (mean 8·5) after anterior infarction. They were started on propranolol or placebo according to a separate random code for each centre, with a dose of 40 mg propranolol thrice daily. Follow-up was at one, three, six, and nine months in 28 centres (Table 1). Outpatient facilities were restricted in 21 hospitals

Table 1 *Number of patients*

	Patients in trial	
	Placebo	*Propranolol*
Entry	365	355
1 month	345	328
3 months	295	299
6 months*	147	146
9 months*	122	123

* In a total of 374 patients the trial duration was only three months.
Mean duration in trial: patients on propranolol 172 days;
patients on placebo 169 days.

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and so hospital follow-up was made at one and three months only. Subsequent mortality and morbidity in patients beyond three months from these 21 centres was ascertained by direct communication with the doctor and, if necessary, with the patient's general practitioner. At the hospital visits blood pressure, heart rate, side effects, and drug compliance were recorded. Patients withdrawn for various reasons were also followed up and their fate determined.

PATIENT SELECTION

Diagnosis of anterior myocardial infarction was based on electrocardiographic abnormalities of an anterior infarction defined as "very probable" on WHO electrocardiographic criteria,[16] plus either a typical history or serum enzyme levels (AST and LDH) at least twice the accepted upper limit of normal or three times if CK was used.

Critera for exclusion included:* (1) bronchospasm; (2) atrioventricular block greater than first degree; (3) sinus bradycardia (<55/minute); (4) persistent heart failure; and (5) beta blockade at time of infarction.

Withdrawal criteria: (1) angina requiring treatment with a beta blocker; (2) bradycardia less than 50 beats/min or heart block greater than first degree; (3) other clinical indications, for example heart failure; and (4) discontinuation of treatment for more than 10 days.

STATISTICAL METHODS

It was estimated that 1000 patients in each group would be needed to give adequate power to detect a reduction in three month mortality from 4 per cent in the placebo group to 2 per cent in the propranolol group[17]; this assumed reduction was based on the earlier practolol trial results.[13] A precautionary sequential analysis of mortality was also used to avoid excessive prolongation of the study. Analysis of mortality included all deaths in all randomised patients, whether or not they withdrew from the trial. Analysis of potential risk factors and their interaction with treatment was carried out by means of stepwise regression,[18] and confirmed by means of Cox's proportional hazard regression model.[19] In stepwise regression the most significant factors are deliberately selected from a large set of possible factors. This leads to significance levels which are too high and which, therefore, must be interpreted cautiously.[20] *

Results

GROUP COMPARISON

The two groups were similar in all the factors shown in Table 2.

TRIAL TERMINATION

When the double-blind trial reached the statistical end-point of no difference, patient recruitment was stopped.

TOTAL DEATHS AND REINFARCTIONS

The difference in total mortality between the two double-blind groups was not statistically significant (Table 3). The 90 per cent confidence limits on the mortality difference in the trial ranged from a 41 per cent decrease to a 54 per cent increase. There were no significant intergroup differences for timing or mode of death or reinfarction (Tables 3 and 4).

Table 2 *Comparability of groups*

History before infarct	*Placebo*	*Propranolol*
No. of patients	365	355
Mean age (y)	54·8	55·0
Percentage male	83	86
Percentage female	17	14
Mean weight (kg)	72	73
Mean height (cm)	170	170
Previous angina:		
Percentage positive	40	35
Percentage with angina more than three months	19	15
Previous infarct (%)	16	15
History of cardiac failure (%)	2	1
Concurrent disease:		
Percentage hypertension	15	13
Percentage peripheral artery disease	2	1
Percentage with diabetes	4	3
Smokers (%)	65	64
Data on original infarct and post-infarct state		
Earliest mean (±SE) systolic and diastolic blood pressure after infarct (mmHg)	144·5 (1·4) 91·4 (0·9)	142·7 (1·3) 91·4 (0·8)
Earliest mean (±SE) heart rate (beats/min)	84·0 (1·0)	82·2 (0·9)
Treatment during acute phase:		
Percentage DC shock	4	5
Percentage drug treatment other than beta blockers	88	86
Percentage receiving beta blockers	7	5
Percentage with cardiac failure in acute phase	21	19
Mean no. of days from infarct to entry	8·4	8·4
Mean (±SE) systolic BP at entry (mmHg)	124·2 (1·0)	122·8 (0·9)
Mean (±SE) diastolic BP at entry (mmHg)	79·7 (0·6)	79·2 (0·6)
Mean (±SE) heart rate at entry	81·9 (0·6)	81·3 (0·7)
Percentage with ventricular ectopics at entry	7	6

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* Full details available on request from Dr N S Baber, ICI Pharmaceuticals.

Table 3 *Total deaths and reinfarctions in all randomised patients at 9 months*

	Placebo		*Propranolol*	
	No.	*Per cent*	*No.*	*Per cent*
Cardiac deaths in trial	18	4·9	19	5·4
Non-cardiac deaths in trial	2	0·5	3	0·8
Cardiac deaths after withdrawal	7	1·9	6	1·7
Non-cardiac deaths after withdrawal	0	0	0	0
Total deaths	27	7·4	28	7·9
Non-fatal reinfarctions in trial	14	3·8	15	4·2
Non-fatal reinfarctions after withdrawal	1	0·3	0	0

Per cent expressed as a percentage of number entering the study.

Table 4 *Time from entry to death—total mortality*

Time from entry (months)	*Placebo*	*Propranolol*
1	14	18
1 to 3	6	3
3 to 6	6	4
6 to 9	1	3

PROGNOSTIC FACTORS AND RELATION TO TREATMENT

Six prognostic factors independent of a treatment effect were identified (Table 5). The overall mortality correlated positively with age and with entry heart rate. Mortality was also higher in patients with arrhythmias at entry.

Attempts were made to relate any effect of treatment on mortality to the six prognostic factors above and also to other factors such as blood pressure (Table 6) (immediately on admission and at entry) and congestive cardiac failure (Table 7). However, no statistically significant relation was found for any of the factors ($p > 0{\cdot}05$).

Table 5 *Risk factors for mortality independent of treatment*

Age	Definite $p < 0{\cdot}005$
Heart rate at trial entry	
Arrhythmias at entry	
Female sex	Possible $p < 0{\cdot}1$
Smoking	
History of myocardial infarction	

Table 6 *Deaths related to acute systolic and entry diastolic blood pressures*

	Placebo	*Propranolo*
No. (%) deaths with acute systolic blood pressure above mean	14 (8·2)	10 (6·7)
No. (%) deaths with acute systolic blood pressure below mean	13 (6·7)	18 (8·8)
No. (%) deaths with entry diastolic blood pressure above mean	21 (9·5)	15 (7·3)
No. (%) deaths with entry diastolic blood pressure below mean	6 (4·2)	13 (8·7)

Table 7 *Death rate by signs of congestive cardiac failure in acute phase*

	Placebo		*Propranolol*	
	No.	*Per cent*	*No.*	*Per cent*
Congestive cardiac failure:				
Absent	22	7·6	21	7·3
Present	5	6·5	7	10·6

WITHDRAWALS (Table 8)

There were no statistically significant differences between the two groups.

OPEN TRIAL

In parallel with the double-blind, placebo-controlled trial, an open study, using 40 mg propranolol three times a day, was also conducted in 500 patients by doctors in 37 hospitals who, because of the practolol multicentre trial findings,[13] were unwilling to consider randomising. There were three findings of particular interest from this study:

(1) Comparability of patients at trial entry (8·5 days) with both groups of the double-blind trial.
(2) A similar total mortality (31/501 entered: 6·2%) at nine months.
(3) A more precise estimate of risk factors independent of treatment was possible by inclusion of this group (Table 5).

Table 8 *Reasons for withdrawal from trial (these are not mutually exclusive)*

	Placebo	*Propranolol*
Reinfarction	9	10
Cardiac failure	22	22
Cardiac failure alone	17	10
Angina	13	7
Arrhythmias	11	7
Adverse reaction	5	12
Other	38	42
Total number of patients withdrawn	88 (24%)	82 (23%)

Discussion

The findings indicate no difference in mortality throughout the nine months of follow-up after anterior myocardial infarction, between those given propranolol (40 mg thrice daily) and placebo. These results merit close examination, because they demonstrate some important features in the design, execution, and interpretation of such trials.

The design of the study took into account the experience gained from the practolol multicentre study.[13] The number of patients required was estimated on the basis that propranolol might produce a comparable reduction in mortality to that of practolol, that is 50 per cent.

Propranolol may produce a reduction in mortality of less than 50 per cent, and this is still possible within the confidence limits of the result (Fig). The dismissal of potentially useful agents because of an inadequate sample size or the reporting of "no difference" between treatment and control when only very large differences have been considered, has been recently reviewed.[21] In the example given in that reference (which was a propranolol post-infarction trial) there was a 77 per cent risk of missing a real difference of 25 per cent reduction in mortality, and a 42 per cent risk of missing a difference of 50 per cent. The Figure gives the 90 per cent confidence limits for the true percentage difference in mortality rates for all propranolol trials. In seven of the eight trials, a 25 per cent reduction in mortality cannot be excluded; in six of the eight studies, a 50 per cent reduction cannot be excluded.

In the present study the lower confidence limit does not exclude a possible reduction of 40 per cent but much larger numbers of patients would have been required to show this smaller difference (approximately 1700 per group). It is pertinent to ask whether a smaller reduction in mortality, if proven, would warrant the widespread use of a beta-blocking agent for all anterior infarction patients. A recent editorial by Rose[22] develops this argument. The annual mortality after an uncomplicated anterior infarction is about 6 per cent,[13] and if a 30 per cent reduction in this mortality could be achieved, then in every 100 patients treated, two patients would benefit.

Another consideration concerns the possibility that harm to specific patient subgroups outweighs benefit to others. However, this was not shown in this trial. In particular, there was no evidence that more patients died in congestive cardiac failure or were withdrawn from the trial because of this complication in the propranolol group compared with placebo.

In the practolol multicentre study, patients with an anterior infarction whose trial entry diastolic blood pressure was equal to or below the mean (78 mmHg) and who received practolol, had only one-sixth the mortality, compared with their respective placebo group (24 deaths on placebo versus four deaths on practolol). Interactions of blood pressure and treatment were sought in the present study, but none of these reached significance at the 5 per cent level.

Detailed comparison with the practolol trial is not appropriate, but possible pertinent differences include: size of trials, differences between patient groups, differences in pharmacological profiles, and differences in the time courses of beta blockade.[23] [24]

We are grateful to Dr K Green and Mr S H Ellis for advice.

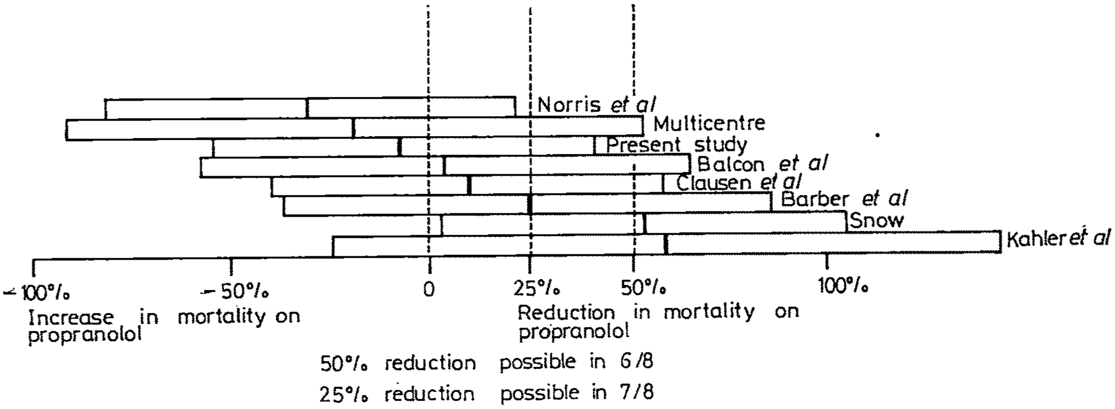

Fig. *Difference in mortality rates with 90 per cent confidence limits expressed as a percentage of observed control rate in eight controlled trials of propranolol.*

References

1 Snow PJD. Effect of propranolol in myocardial infarction. *Lancet* 1965; **ii:** 551–3.

2 Balcon R, Jewitt DE, Davies JPH, Oram S. A controlled trial of propranolol in acute myocardial infarction. *Lancet* 1966; **ii:** 917–20.

3 Clausen J, Felsby M, Schønau Jørgensen F, Lyager Nielsen B, Roin J, Strange B. Absence of prophylactic effect of propranolol in myocardial infarction. *Lancet* 1966; **ii:** 920–4.

4 Multicentre trial. Propranolol in acute myocardial infarction. *Lancet* 1966; **ii:** 1435–8.

5 Barber JM, Murphy FM, Merrett JD. Clinical trial of propranolol in acute myocardial infarction. *Ulster Med J* 1967; **36:** 127–30.

6 Sloman G, Stannard M. Beta-adrenergic blockade and cardiac arrhythmias. *Br Med J* 1967; **iv:** 508–12.

7 Kahler RL, Brill SJ, Perkins WE. The role of propranolol in the management of acute myocardial infarction. In: Kattus AA, Ross G, Hall VE, eds. *Cardiovascular beta-adrenergic responses*. Los Angeles: University of California Press, 1970: 213.

8 Norris RM, Caughey DE, Scott PJ. Trial of propranolol in acute myocardial infarction. *Br Med J* 1968; **ii:** 398–400.

9 Fuccella LM. Report on the double-blind trial with compound CIBA 39 089-Ba (Trasicor), in myocardial infarction. Quoted by Sowton E. Beta adrenergic blockade in cardiac infarction. *Prog Cardiovasc Dis* 1968; **10:** 561–74.

10 Reynolds JL, Whitlock RML. Effects of a beta-adrenergic receptor blocker in myocardial infarction for one year from onset. *Br Heart J* 1972; **34:** 252–9.

11 Wilhelmsson C, Vedin JA, Wilhelmsen J, Tibblin G, Werkö L. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. *Lancet* 1974; **ii:** 1157–60.

12 Ahlmark G, Saetre H, Korsgren M. Reduction of sudden deaths after myocardial infarction (letter). *Lancet* 1974; **ii:** 1563.

13 Multicentre International Study. Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. *Br Med J* 1975; **iii:** 735–40.

14 Barber JM, Boyle DM, Chaturvedi NC, Singh N, Walsh MJ. Practolol in acute myocardial infarction. *Acta Med Scand* 1975; suppl 587: 213–9.

15 Norris RM, Clarke ED, Sammel NL, Smith WM, Williams B. Protective effect of propranolol in threatened myocardial infarction. *Lancet* 1978; **ii:** 907–9.

16 World Health Organization. The electrocardiogram in coronary heart disease. *WHO Tech Rep Ser* 1959; **168:** 25–8.

17 Burdette WJ, Gehan EA. *Planning and analysis of clinical studies*. Springfield, Illinois: Charles C Thomas, 1970: 36.

18 Draper NR, Smith H. *Applied regression analysis*. New York: John Wiley, 1966: 163.

19 Cox DR. Regression models and life tables. *J R Stat Soc* 1972; **B34:** 187.

20 Pope T, Webster JT. The use of an F-statistic in stepwise regression procedures. *Technometrics* 1972; **14:** 327.

21 Freiman JA, Chalmers TC, Smith H Jr, Kuebler RJ. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial: survey of 71 "negative" trials. *N Engl J Med* 1978; **299:** 690–4.

22 Rose G. Population screening for myocardial ischemia. *Am Heart J* 1978; **96:** 427–9.

23 Bodem G, Chidsey CA. Pharmacokinetic studies of practolol, a beta adrenergic antagonist in man. *Clin Pharmacol Ther* 1973; **14:** 26–9.

24 Carruthers SG, Kelly JG, McDevitt DG, Shanks RG, Walsh MJ. Blood levels of practolol after oral and parenteral administration and their relationship to exercise heart rate. *Clin Pharmacol Ther* 1974; **15:** 497–509.

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Left ventricular function and beta-blockade in chronic ischaemic heart failure

Double-blind, cross-over study of propranolol and penbutolol using non-invasive techniques

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SUMMARY From an original group of 32 male post-infarction patients treated with digoxin for presumed cardiac failure eight patients were recruited for the present study by means of a single-blind evaluation of the patients' clinical need for continued treatment with digoxin. Dyspnoea on effort as recorded on a standardised questionnaire was used to define failure of the left ventricle. In order to be recruited to the present study the functional class (NYHA) of the patients had to deteriorate at least one full class while on placebo instead of digoxin. During a subsequent double-blind, cross-over phase digoxin was kept constant and additional treatment with 160 mg propranolol or 40 mg penbutolol twice daily was given. Each patient received the two beta-blockers for periods of two weeks each separated by an intermediate four-week placebo period. Cardiac function was investigated using electrocardiography, apexcardiography, phonocardiography, echocardiography, and pulse curves from the carotid artery, jugular bulb, and liver before and at the end of each treatment period. The findings indicated well-preserved systolic function before beta-blockade despite the history and symptoms, and despite several indices of cardiac damage such as pronounced ischaemic electrocardiographic abnormalities, and large and hypertrophied hearts (*x*-ray and echo). Instead, many variables reflected impaired diastolic function. During beta-blockade no signs of impaired cardiac function emerged. On the contrary, enhanced diastolic filling properties were found; these also contributed to the performance of the left ventricle during systole. No differences between propranolol and penbutolol could be shown.

Beta-blockers are widely used in the treatment of patients with cardiovascular disease. At present beta-blockers are used for arrhythmias, angina pectoris, hypertension, and, recently, as prophylaxis against sudden death after myocardial infarction.[1 2] On a theoretical basis, symptoms of heart failure have been considered as contraindications to beta-blockade. In our experience, however, heart failure caused by beta-blockade is rare in patients treated with digitalis.[3]

The purpose of the present investigation was to assess any possible negative influence of beta-blockade on left ventricular function in post-infarction patients with chronic left ventricular failure clinically compensated by treatment with digoxin. The study was a double-blind, randomised cross-over study of propranolol and penbutolol using non-invasive techniques to study cardiac function.

Patients and methods

The patients in this study had to complete an initial, single-blind run-in phase in a defined manner in order to establish the clinical indication for continuous treatment with digoxin (Fig. 1). The single-blind phase comprised three stages of six weeks each.

(1) During the first stage all patients were in functional class II because of dyspnoea on effort[4] during treatment with digoxin, 0·25 mg daily.

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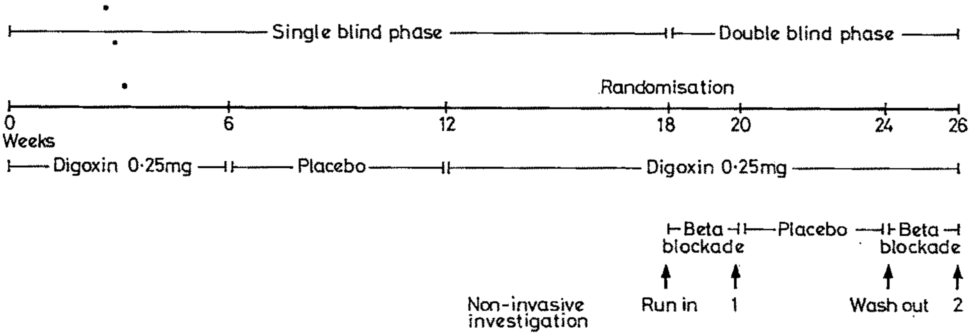

Fig. 1 *Study design. Weekly clinical check-ups took place throughout the study.*

(2) Digoxin treatment was changed to placebo and the functional class was recorded every week during the second stage.

(3) Treatment was then changed back to digoxin 0·25 mg daily for six weeks and the functional class was recorded each week.

The patients who had been consistently worse by at least one functional class during the final four weeks on placebo and reported consistent return to the previous superior functional class during the final four weeks on digoxin were selected for the second double-blind controlled phase of the study. They comprised eight out of the original 32 male patients with sinus rhythm. All had had a definite myocardial infarction from five to 64 months before the investigation. They were seen regularly at the Postmyocardial Infarction Clinic in Göteborg, Sweden, and all were treated acccording to standardised criteria.[5] All patients were free from electrocardiographic conduction defects, angina pectoris, hypertension, and chronic obstructive pulmonary disease. Patient characteristics are listed in Table 1. The patients were seen once a week during the study. The presence of cardiac symptoms was registered by means of standardised questionnaires.[6] During the present study the questionnaires were completed by trained technicians without knowledge of the treatment given. The patients were asked to abstain from alcohol throughout the entire study period and were instructed not to change their coffee, tea, and salt consumption. All patients were fully informed about all aspects of the trial and verbally agreed to participate. The procedure was approved by the local ethical review committee.

The controlled double-blind trial consisted of three parts (Fig. 1). All patients maintained their digoxin treatment unchanged throughout this part of the study. After an initial non-invasive investigation of the cardiac function the patients entered treatment period I. They were randomly allocated to treatment with either 40 mg penbutolol or 160 mg propranolol twice daily for two weeks. At the end of this period another non-invasive investigation of the cardiac function was made.

After treatment period I there was a wash-out

Table 1 *Patient characteristics at entry to double-blind phase of the study*

Case no.	*Age (y)*	*Height (cm)*	*Weight (kg)*	*Months since myocardial infarction*	*Relative cardiac vol (ml/m² BSA)**	*Electrocardiographic abnormality†*	*Echocardiographic thickness (cm)§ Post. wall*	*Septum*
1	61	180	80	16	500	+	‡	‡
2	59	180	82	64	600	+	1·4	1·6
3	52	177	78	25	540	+	1·3	1·5
4	57	178	88	8	700	+	1·5	1·3
5	58	160	70	9	500	+	1·4	1·4
6	51	176	71	6	450	+	1·2	1·3
7	58	175	79	5	500	–	‡	1·9
8	60	170	71	13	450	+	1·2	1·3

* Measured according to Jonsell[15], > 450 ml/m² BSA abnormal.
† Minnesota coded[6] Q-waves 1:1–3 and/or ST-T abnormalities 4:1–3 and/or T-wave abnormalities 5:1–3
‡ Satisfactory echo recordings not obtained.
§ Normal range < 1·2 cm.

period of four weeks. At the end of this period a non-invasive investigation of the cardiac function was made in half the patients to ascertain that the effect of beta-blockade had vanished. All patients could not be studied during this phase because of the great demand on the laboratory of non-invasive investigations from other departments. The patients originally treated with penbutolol or propranolol were then crossed over to the alternative beta-blocker during the subsequent two weeks, treatment period II. At the end of period II the final non-invasive investigation of cardiac function was made. No other concomitant drugs were permitted. All trial drugs were given to the patients in prepared boxes containing separate compartments for each morning and night. Active drugs and placebos were of the same shape, taste, and appearance.

NON-INVASIVE INVESTIGATIONS OF CARDIAC FUNCTION

The patients arrived at the laboratory in the morning after having a light breakfast and after having taken their morning dose of digoxin and the trial drug. All patients arrived at the laboratory at the same time of the week for all the non-invasive investigations during the study.

Conventional electrocardiogram, apexcardiogram, phonocardiograms, pulse curves from the carotid artery, jugular bulb, and liver, and resting blood pressures were all recorded on an ink-jet seven-channel recorder (Siemens-Elema AB, Sweden) in a sound-protected room.

Resting systolic and diastolic blood pressures (phase V) were measured after 45 minutes' rest in the supine position with an automatic device for cuff inflation and deflation, with a microphone placed over the right brachial artery and with simultaneous recording of cuff pressure, Korotkoff sounds, and electrocardiogram.

Echocardiographic recordings were made using commercially available equipment (Brüel-Kjaer, Denmark) connected to a strip chart recorder (Honeywell, USA). The standard technique[7] of examining the diameter of the left atrium and left ventricle was followed. The anteroposterior diameter of the left ventricle was measured just below the aortic root, through or close to both the anterior and posterior mitral leaflets at the end of systole and diastole. When measuring the left atrium the beam had to go through and visualise the aortic leaflets as well. The stroke volume was calculated from the end-diastolic and end-systolic volumes derived by the cube method,[8] and the ejection fraction from the stroke volume and the end-diastolic volume. The mean rate of circumferential fibre shortening was calculated.[9] The left ventricular ejection time in the formula was derived from the carotid pulse curve (corrected to the actual heart rate).

The variables studied were:

(a) Total electromechanical systole from the beginning of the QRS complex to the beginning of the aortic component of the second heart sound (QA_2).

(b) The electromechanical interval from the beginning of the QRS complex to the systolic upstroke of the apexcardiogram (EMI).

(c) The left ventricular ejection time from the beginning of the systolic upstroke of the carotid pulse tracing to the incisura (LVET) and corrected for heart rate (LVET %).[10]

(d) The pre-ejection period ($PEP = QA_2 - LVET$).

(e) The isovolumetric contraction time ($ICT = PEP - EMI$).

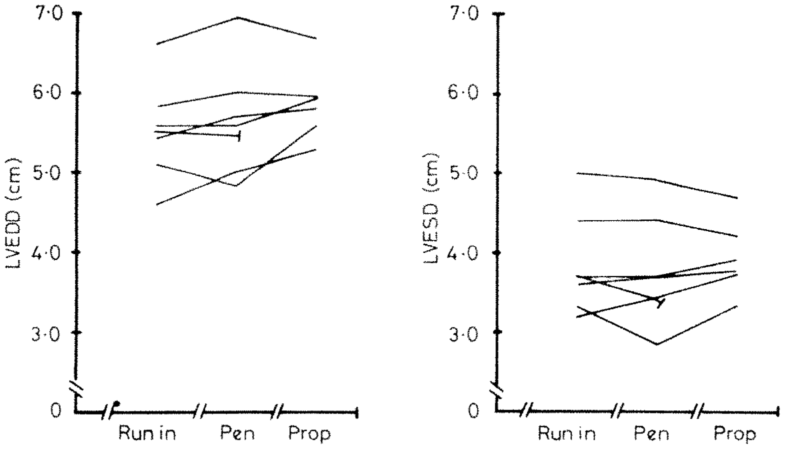

Fig. 2 *Individual measurements of LVEDD and LVESD during run-in and after penbutolol (Pen) and propranolol (Prop). Values for seven patients in one of whom complete measurements could not be obtained.*

(f) The PEP/LVET ratio.
(g) The ICT/LVET ratio.
(h) The interval between the aortic component of the second sound and the 0 point of the apexcardiogram (A_2O).
(i) Pressure rise velocity during the isovolumetric contraction time, that is DBP/ICT.
(j) The total interval from the beginning of QRS to the opening of the mitral valve (QM_0).
(k) The ratio (%) of the amplitude of the "a" wave (a) and the total deflection of the apex cardiogram (H; a/H ratio).
(l) The ratio (%) of the rapid filling wave (RFW/H ratio).
(m) The amplitude of the fourth sound in the 50 Hz band relative to that of the first sound ($IV/I_{50\,Hz}$).
(n) Left ventricular end-diastolic diameter (LVEDD).
(o) Left ventricular end-systolic diameter (LVESD).
(p) Echocardiographic stroke volume (SV).
(q) Echocardiographic ejection fraction (EF).
(r) Echocardiographic mean ventricular circumferential fibre shortening (mean V_{CF}).
(s) Echocardiographic left atrial diameter (LA).

Analysis and calculation of each variable was done blindly without knowledge of the treatment or study period. All variables were derived as the mean of measurements from five consecutive beats. All methods used and the definitions of the measurement points on the electrocardiogram, phonocardiogram, carotid pulse tracing, apexcardiogram, and echocardiogram have been presented in detail elsewhere.[10–13]

Because of the small number of patients and the abnormal distributions of many variables, differences between the groups were tested by the Friedman two-way analysis of variance. Thereafter differences between two groups were tested by the Wilcoxon signed pairs rank sum test.[14]

Statistically significant differences were considered for $p<0·05$. Findings with a $p<0·1$ were considered biologically meaningful if consistent in other related variables and similarly observed after both beta-blockers.

Results

There were no significant differences between the run-in and wash-out measurements. Therefore, the wash-out results have been omitted. The results are presented in Table 2.

CARDIAC FUNCTION BEFORE BETA-BLOCKADE

The patients had several signs of myocardial damage with electrocardiographic abnormalities, enlarged hearts, and myocardial hypertrophy (Table 1). Six out of eight patients had abnormally prolonged EMI but otherwise the indices of systolic function showed signs of little or no impairment as indicated by findings of normal LVET per cent, PEP/LVET, and high DBP/ICT. A clearly reduced EF and mean V_{CF} was found in only two patients. However, the diastolic function

Table 2 *Results of non-invasive cardiac function studies before (run-in) and after two weeks of penbutolol or propranolol in eight patients with chronic congestive failure after myocardial infarction treated with digoxin.*

Variable	*Run-in*	*Penbutolol*	*Propranolol*	*Probability*	*Normal range*
SBP (mmHg)	127 (116–163)	123 (97–164)	120 (107–150)	NS	—
DBP (mmHg)	85 (70–95)	76 (66–97)	75 (71–92)	NS	—
HR/min	58 (48–92)	54 (40–59)	53 (42–66)	< 0·05	—
QA_2 (ms)	395 (356–425)	421 (391–458)	414 (382–434)	< 0·05	—
EMI (ms)	45 (34–72)	42 (28–69)	45 (25–74)	NS	< 40
LVET (ms)	300 (247–321)	314 (283–342)	315 (257–327)	< 0·05	—
LVET (%)	98 (94–105)	98 (95–112)	97 (90–111)	NS	> 90
PEP (ms)	98 (81–117)	109 (79–131)	102 (81–125)	NS	< 130
PEP/LVET	0·32 (0·26–0·44)	0·34 (0·26–0·45)	0·34 (0·23–0·49)	NS	< 0·45
ICT (ms)	49 (31–83)	67 (40–74)	57 (37–76)	NS	< 100
ICT/LVET	0·16 (0·11–0·20)	0·22 (0·13–0·24)	0·19 (0·11–0·34)	NS	< 0·35
A_2O (ms)	176 (149–198)	178 (150–190)	177 (158–189)	NS	< 150
QM_0 (ms)	476 (385–499)	473 (391–520)	472 (407–535)	NS	Not defined
DBP/ICT (mmHg/s)	1600 (1145–2452)	1210 (1029–1650)	1422 (1211–1919)	NS	775–1200
a/H (%)	7·0 (3·5–26·0)	10·5 (4·6–26·5)	7·5 (2·4–24·3)	NS	< 15
RFW/H (%)	3·6 (1·2–20·9)	3·7 (1·1–12·2)	4·2 (2·7–8·1)	NS	< 5
IV/I50Hz (%)	10·9 (4·0–24·3)	6·3 (2·9–18·4)	8·0 (3·4–10·2)	< 0·02	< 20
LA (cm)	4·2 (3·8–6·0)	4·4 (3·9–6·0)	4·3 (3·8–6·1)	NS	< 4·0
LVEDD (cm)	5·5 (4·6–6·6)	5·7 (4·8–6·9)	5·9 (5·3–6·7)	< 0·06	< 5·6
LVESD (cm)	3·7 (3·2–5·0)	3·6 (2·8–4·9)	3·9 (3·3–4·4)	NS	—
SV (ml)	100 (64–110)	128 (86–211)	138 (98–197)	< 0·1	—
CO (l/min)	6·5 (3·3–10·5)	6·7 (3·7–12·4)	7·7 (4·6–9·5)	< 0·1	—
EF (%)	0·67 (0·56–0·73)	0·70 (0·61–0·80)	0·68 (0·64–0·80)	< 0·1	> 0·60
Mean V_{CF} (circ/s)	1·01 (0·83–1·23)	1·10 (0·86–1·16)	1 06 (0·96–1·26)	NS	> 1·0

Median values and observed range within parentheses. Normal ranges according to Wikstrand,[10 11] and Swedberg.[13]

was more compromised in a number of patients as indicated by findings of abnormal prolongation of $A_2 0$ in seven, abnormally large LA in six, and abnormally high a/H ratio or $IV/I_{50\,Hz}$ in four of the patients.

CARDIAC FUNCTION AFTER BETA BLOCKADE

Blood pressure and heart rate

Penbutolol and propranolol did not reduce the systolic or diastolic blood pressures. The heart rate was reduced equally by penbutolol and propranolol.

Systolic and diastolic time intervals

QA_2 was equally prolonged by both penbutolol and propranolol because of a prolongation of LVET. This prolongation was caused by the decrease in heart rate since LVET per cent was not influenced.

Phono- and apexcardiographic measurements

The $IV/I_{50\,Hz}$ was lowered by beta blockade. The four patients with a/H ratios above 15 per cent at run-in returned to normal during beta-blockade. The reduction was most pronounced when the comparison was made between run-in values and propranolol. No patient had a pathological third heart sound.

Echocardiographic measurements

Left atrial diameter was not affected by beta-blockade. LVEDD was increased by both beta-blockers, the difference being most pronounced between run-in values and propranolol. LVESD was not affected by beta blockade but tended to be reduced by penbutolol compared with propranolol.

Stroke volume was increased by beta-blockade. This difference was more pronounced for propranolol. The effect on stroke volume was sufficient to cause an increased cardiac output despite the lowered heart rate. Ejection fraction was improved by both beta-blockers. Mean V_{CF} was not changed by beta-blockade.

Comparison between penbutolol and propranolol

No consistent differences between the two beta blockers were observed.

Clinical observations and side effects

The body weight of the patients was not changed. Four patients spontaneously reported less dyspnoea on exertion while on beta-blockers in contrast to placebo; this improvement was reflected in statements of an increased level of physical performance. No patient reported an increase of dyspnoea on effort during beta blockade.

Discussion

The eight patients of the present study all had a clinically verified indication for digoxin. This was checked because of the conflicting opinions on the role of digoxin for heart failure in patients with sinus rhythm. The design of the study and the doses of the beta blockers used were such that any serious negative effects of these agents would most probably have been disclosed.

In the diagnosis of left ventricular dysfunction the systolic time intervals alone do not provide enough information.[10] More complete information is required on the size of the left ventricle and left atrium, the filling pattern of the left ventricle, contractility, and valvular function. This can be obtained by combining echocardiography, phonocardiography, apexcardiography, and recording of systolic and diastolic time intervals. Pathological systolic time intervals appear at a late stage in left ventricular dysfunction since the altered filling pattern during diastole and ventricular hypertrophy may compensate for the impaired systolic left ventricular function.[10,16,17] Therefore, diastolic function must also be studied when impairment of the left ventricular function is considered.

Invasive assessment of left ventricular function may have yielded interesting data for correlation with the present non-invasive findings. Catheterisation and angiocardiography were, however, not performed as it was not considered ethically justifiable to perform repeated invasive investigations in our patients. Regardless of whether invasive or non-invasive methods have been used, there is

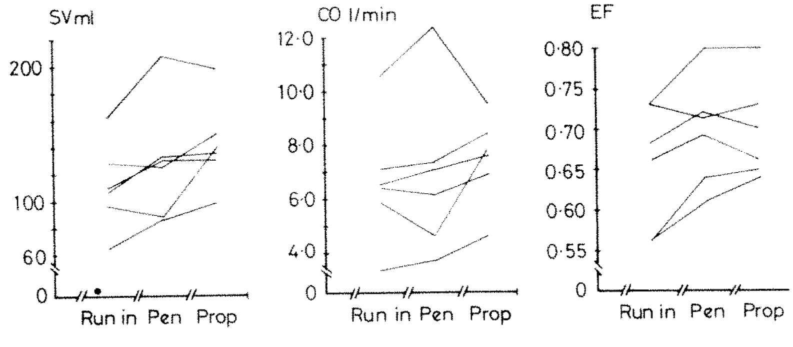

Fig. 3 *Individual measurements of stroke volume (SV), cardiac output (CO), and ejection fraction (EF) during run-in and after penbutolol (Pen) and propranolol (Prop). Values for six patients with complete sets of measurements.*

a lack of agreement on universally accepted indices of the function of the left ventricle during the various intervals of the cardiac cycle.

The various measurements recorded in the present study have been analysed with particular attention to consistent changes in related measurements, and special importance has been attached to changes observed during treatment with both of the two beta-blockers. In addition, special attention was paid to detecting adverse effects of beta-blockade on cardiac function. This type of pattern-recognition analysis has previously been used in our laboratory.[10 11 13 18]

Propranolol lacks intrinsic stimulating activity and penbutolol is a more recent non-selective beta-blocker with an intrinsic stimulating activity of approximately 15 per cent.[19] The doses were considered equipotent in the reduction of exercise tachycardia.[20]

The finding of predominant impairment of diastolic cardiac function in our patients is in agreement with an earlier study. The results regarding pressure rise velocity (DBP/ICT) may be interpreted as showing that the contraction may have been more powerful in several postinfarction patients compared with reference subjects. This observation could not be explained by treatment with digitalis, nor could it be explained by differences in the end-diastolic pressure as judged from the a/H ratio from the apexcardiogram.[10] Patients with a much higher diastolic pressure may, however, have a normal "a" wave in the apexcardiogram.[21]

In the present study the non-invasive signs of improved pump function after beta-blockade as reflected by increased stroke volume, cardiac output, and ejection fraction were the result of an increased LVEDD but an essentially unchanged LVESD. End-systolic dimensions have been shown to discriminate patients with different degrees of impaired left ventricular function.[22] These findings may support the interpretation of our data that the working point of the left ventricle was shifted to a more favourable position on the Starling curve. Thus there were no signs of impaired systolic function during beta-blockade in our patients. Some patients may have had asymmetric ventricular contractions caused by local dyskinesia. Because the patients constituted their own controls the changes observed should be valid, though absolute individual levels may be false. In particular, the calculations of stroke volume and cardiac output must be interpreted with caution but ejection fraction is more reliable since similar errors are introduced in both the numerator and the denominator.

The ratio PEP/LVET has been found to be closely correlated with the contractility index of the left ventricle.[23 24] This ratio was not significantly influenced by beta-blockade nor was ICT nor DBP/ICT. A measure of the duration of the relaxation between closure of the aortic and opening of the mitral valves can be constructed as the difference $QM_0 - QA_2$. The interval tended to be shorter during beta-blockade, demonstrating a faster rate of relaxation despite the lowering of the heart rate; this indicates a more favourable situation regarding the time for left ventricular filling. Improved filling of the left ventricle during the rapid and slow-filling phase may explain the signs of a less vigorous atrial contraction after beta-blockade as indicated by the constant a/H ratio and lowered $IV/I_{50\,Hz}$. If in ischaemia the supply and demand of calcium or ATP are barely balanced during the systolic contraction, a relative deficiency of ATP with delayed inactivation of calcium might arise leading to delayed relaxation.[25 26] The contraction phase and the relaxation phase can be influenced partly independently of one another.[27–29] The findings in our study might indicate a direct influence of the beta-blockers on cellular function during relaxation.

In severe congestive cardiomyopathy some patients have improved dramatically when they were treated with beta-blockade. The individual response, however, is variable. [13 18] The mechanism of action of beta-blockers in this condition is probably somewhat different from that in our patients.

Dyspnoea on effort is the symptom defining the clinical entity of cardiac failure in the present study. In patients without pulmonary disease dyspnoea on effort may be caused by increased pulmonary capillary pressure reflecting an increased filling pressure of the left ventricle. The increased filling pressure may in turn be a result of left ventricular systolic dysfunction or diastolic dysfunction (left ventricular distensibility) or a combination thereof. In patients with decreased left ventricular distensibility, an increased filling time may compensate for the difficulty in filling the ventricle. The situation is analogous to that in mitral stenosis where stroke volume decreases with increasing heart rate because the degree of filling of the left ventricle is more time-dependent than under normal conditions. The major functional impairment after not too extensive infarction may not be in emptying the ventricle but rather in a decreased filling capacity caused by hypertrophy, fibrosis, or scarring. Well-preserved systolic contractile function in intact parts of the myocardium may compensate for dyskinetic areas. This hypothesis is supported by the present findings together with those in a previous study.[10] It may contribute to the explanation as to why precipitation of failure is rarely seen after beta-blockade. The lowering of the heart rate after beta-blockade may, therefore, improve the cardiac function and symptoms in many post-myocardial infarction patients. There may also be a direct effect of beta-blockers on left ventricular distensibility.

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References

1 Wilhelmsson C, Vedin A, Wilhelmsen L, Tibblin G, Werkö L. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. *Lancet* 1974; **ii:** 1157–60.
2 Multicentre International Study. Improvement in prognosis of myocardial infarction by long-term beta-adrenoceptor blockade using practolol. *Br Med J* 1975; **iii:** 735–40.
3 Vedin A, Wilhelmsson C. Angina pectoris, hypertension, decompensation and return to work during two years' follow-up. *Acta Med Scand* 1975; suppl 575: 25–30.
4 New York Heart Association Criteria Committee. *Diseases of the heart and blood vessels. (Nomenclature and criteria for diagnosis.)* 6th ed. Boston: Little Brown, 1964.
5 Elmfeldt D, Wilhelmsen L, Tibblin G, Vedin A, Wilhelmsson C, Bengtsson C. A post-myocardial infarction clinic in Göteborg. A follow-up of MI patients in a specialized out-patient clinic. *Acta Med Scand* 1975; **197:** 497–502.
6 Rose G, Blackburn H. *Cardiovascular survey methods.* Geneva: WHO, 1968: 80–5.
7 Feigenbaum H. *Echocardiography.* Philadelphia: Lea & Febiger, 1972.
8 Pombo JF, Troy BL, Russel RO. Left ventricular volume and ejection fraction by echocardiography. *Circulation* 1971; **43:** 480–90.
9 Cooper RH, O'Rourke RA, Karliner JS, Peterson KL, Leopold G. Comparison of ultrasound and cineangiographic measurement of the mean rate of circumferential fibre shortening in man. *Circulation* 1972; **46:** 914–23.
10 Wikstrand J, Berglund G, Wilhelmsen L, Wallentin I. Value of systolic time intervals. *Br Heart J* 1978; **40:** 256–67.
11 Wikstrand J. *Non-invasive assessment of cardiac function.* Göteborg, Sweden: Thesis. 1976.
12 Wikstrand J, Nilsson K, Wallentin I. Distortion of non-invasive cardiac pulse curves. A capillary damped pick-up and a calibration unit for apex cardiograms and other pulse curves. *Br Heart J* 1977; **39:** 995–1005.
13 Swedberg K. *Congestive cardiomyopathy.* Göteborg, Sweden: Thesis. 1978: 1–172.
14 Siegel AJ. *Non-parametric statistics for the behavioural sciences.* New York: McGraw Hill, 1956.
15 Jonsell S. A method for determination of the heart size by teleroentgenology (a heart volume index). *Acta Radiol (Stockh)* 1939; **20:** 325–40.
16 Rackley CE, Hood WP, Rolett EL, Young DT. Left ventricular end-diastolic pressure in chronic heart disease. *Am J Med* 1970; **48:** 310–19.
17 Dodge HT. Hemodynamic aspects of cardiac failure. In: Braunwald E, ed. *The myocardium, failure and infarction.* New York: HP Publishing, 1973.
18 Waagstein F, Hjalmarsson Å, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br Heart J* 1975; **37:** 1022–36.
19 Nyberg G, Vedin A, Wilhelmsson C. The intrinsic sympathomimetic activity in penbutolol. *Eur J Clin Pharmacol* 1979; **16:** 381–6.
20 Johansson SR, McCall M, Wilhelmsson C, Vedin A. The duration of action of different beta-blockers. *Clin Pharmacol Ther* 1980; **27:** 593–601.
21 Voigt GC, Friesinger H. The use of apexcardiography in the assessment of left ventricular diastolic pressure. *Circulation* 1970; **41:** 1015–24.
22 Grossman W, Braunwald E, Mann T, McLaurin LP, Green LH. Contractile state of the left ventricle in man as evaluated from end-systolic pressure—volume relations. *Circulation* 1977; **56:** 845–52.
23 Garrard CL, Weissler AM, Dodge HT. The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. *Circulation* 1970; **42:** 455–62.
24 Ahmed SS, Levinson GE, Schwartz CJ, Ettinger PO. Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man. *Circulation* 1972; **46:** 559–71.
25 Fogelman AM, Abbasi AS, Pearce ML, Kattus AA. Echocardiographic study of the abnormal motion of the posterior left ventricular wall during angina pectoris. *Circulation* 1972; **42:** 455–62.
26 Kovick RB, Fogelman AM, Abbasi AS, Peter JB, Pearce ML. Echocardiographic evaluation of posterior left ventricular wall motion in muscular dystrophy. *Circulation* 1975; **52:** 447–54.
27 Parmley WW, Sonnenblick EH. Relation between mechanics of contraction and relaxation in mammalian cardiac muscle. *Am J Physiol* 1969; **216:** 1084–91.
28 Cohn PF, Liedtke AJ, Serur J, Sonnenblick EH, Urschel CW. Maximal rate of pressure fall (peak negative dP/dt during ventricular relaxation. *Cardiovasc Res* 1972; **6:** 263–7.
29 Meerson FZ, Kapelko VI. The significance of the inter-relationship between the intensity of the contractile state and the velocity of relaxation in adapting cardiac muscle to function at high loads. *J Mol Cell Cardiol* 1975; **7:** 793–806.

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An unusual case of large right atrial myxoma

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SUMMARY A case of right atrial myxoma is described. The patient had vague and variable symptoms and it was not until five years after first presentation that she had developed clinical and electrocardiographic evidence of right atrial hypertrophy, and angiocardiographic evidence of a fist-sized myxoma which was subsequently removed surgically.

Although 75 per cent of cardiac myxomata occur in the left atrium, there are many reports of right atrial myxoma.[1 2] Symptoms of exertional dyspnoea, weakness, and fatigue are frequent and have been related to a reduction in cardiac output[2] which has been confirmed at cardiac catheterisation in some instances.[3 4] These symptoms are, however, usually accompanied by signs of obstruction to right atrial outflow.[2 5] We describe a patient who first presented with variable symptoms of weakness, malaise, and dizziness in the absence of physical signs or electrocardiographic abnormalities. Though several medical practitioners referred to her bizarre symptoms, the diagnosis of right atrial myxoma was not made until the development of abnormal physical signs and an abnormal electrocardiogram.

Case report

A 28-year-old woman, a typist, complained of several episodes of light-headedness, sweating, breathlessness, and weakness which lasted up to 30 minutes and were usually unrelated to exercise. She was referred to a consultant cardiologist who found no clinical, radiological, or electrocardiographic abnormalities.

The most impressive feature of the interview was her pronounced agitation and distress upon seeing a dead cockroach under the consultation couch which led to an attack similar to those she had experienced previously. A diagnosis of hysterical hyperventilation resulting from a personality disorder was made at that time, but no further investigations were performed to substantiate this.

In the following year she was referred to a gynaecology department for investigation of amenorrhoea, which was attributed to discontinuing an oral contraceptive. The amenorrhoea persisted, but when she and her husband eventually decided after another four years that they did not want any children, she was admitted for bilateral tubal ligation. Several doctors again commented on her bizarre personality, but it was also noted that she had a systolic murmur and she was referred to the cardiology clinic, by then five years after her original appointment.

She complained of further attacks similar to those described earlier, but they were more frequent and more severe. During such an episode she would "feel like a jelly", with extreme tiredness and light-headedness, was sometimes breathless, and usually felt as though she wanted to close her eyes and sleep. Attacks occurred both on exercise and at rest and she frequently had to sit or even lie down in a shop on the way to work if she felt unwell. If they occurred at home, she would lie face down on a bed for 30 minutes after which time she improved, but sometimes she felt unwell for as long as 12 hours. Between attacks she felt well for periods of up to several weeks and she regularly took part in vigorous exercise.

By then, however, there were several abnormal features. There was a very prominent "a" wave in the jugular venous pulse and also a scratchy intermittent systolic and diastolic murmur, maximal in the fourth intercostal space at the left sternal edge and sounding like a pericardial friction rub or an exocardiac murmur. The electrocardiogram showed very tall P waves in leads II, III, and V1 to V4, indicating right atrial hypertrophy. There was also T wave inversion in V1 to V4 (Fig. 1). The chest *x*-ray film showed a straight heart border, but no increase in heart size.

The erythrocyte sedimentation rate was 60 mm in the first hour and, though the total protein was normal, the albumin fraction was low at 49 per cent, with slightly raised alpha-2 and gamma globulins. The liver was not enlarged but the alkaline phosphatase was raised at 222 units/l (normal 20 to 85 units/l) with an increased liver band on electrophoresis.

At cardiac catheterisation the right atrial "a" wave was 19 mmHg, the right ventricular pressure was 27/10 mmHg, and the pulmonary artery pressure 16/7 mmHg. Cineangiography showed a large filling defect in the right atrial cavity.

Because of the auscultatory evidence which suggested pericarditis, the T wave changes in the right ventricular leads, the raised alkaline phosphatase, and a liver scan reported as showing small metastatic deposits, it was feared that there was a malignant tumour, with right ventricular and pericardial infiltration and hepatic metastases. A liver biopsy, however, showed no evidence of tumour.

At thoracotomy the right atrium was found to be almost completely filled by a large, hard, bluish-purple mass which was slightly lobulated and was attached over a distance of 2 cm to the lateral wall of the atrium. The tumour (Fig. 2) measured $9 \times 8 \times 6$ cm and histological examination confirmed that it was a myxoma. Inspection of the liver showed that it was enlarged and congested, but there was no sign of tumour.

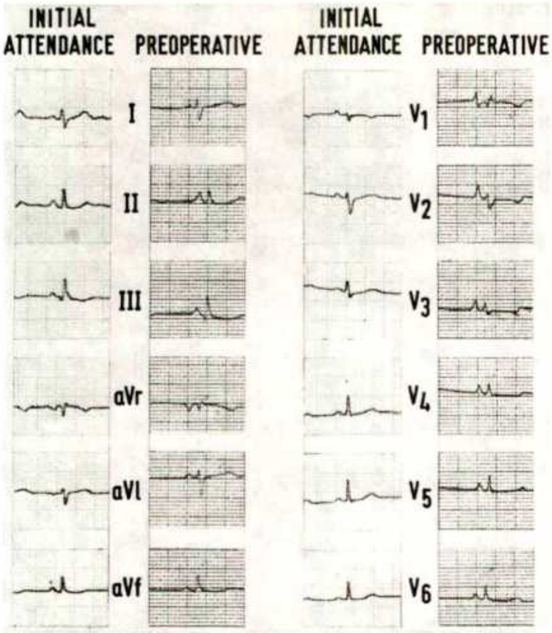

Fig. 1 *Comparison of electrocardiograms from first attendance and five years later, showing the development of large P waves and anterior T wave inversion.*

Postoperatively she recovered satisfactorily; the alkaline phosphatase and liver scan rapidly returned to normal. One year after operation, she was entirely free from symptoms and had a normal venous pressure, no friction rub or murmur, and a normal electrocardiogram and chest *x*-ray. Erythrocyte sedimentation rate and plasma proteins were also normal. She had returned to an active life, her only complaint being that her menstrual periods had restarted.

Discussion

A combination of features (namely what appeared to be a pericardial friction rub, T wave changes in the electrocardiogram, elevation of the alkaline phosphatase, and an abnormal liver scan) suggested the possibility that the filling defect noted on cineangiography was caused by a malignant tumour. Previous case reports of a right atrial myxoma have, however, recorded the presence of what seemed to be a pericardial friction rub[6] though the cause is uncertain. The T wave abnormalities in leads V1 to V4 are unexplained, but similar changes have been observed.[7] It is possible that the raised alkaline phosphatase and perhaps also the liver scan abnormalities were a result of hepatic congestion secondary to obstruction in the right atrium.

The tumour originated from the lateral wall of the atrium, whereas in most reported cases the origin was from the atrial septum in the vicinity of the fossa ovalis.[8] Origin from the free inferolateral wall of the right atrium has, however, been described.[9 10]

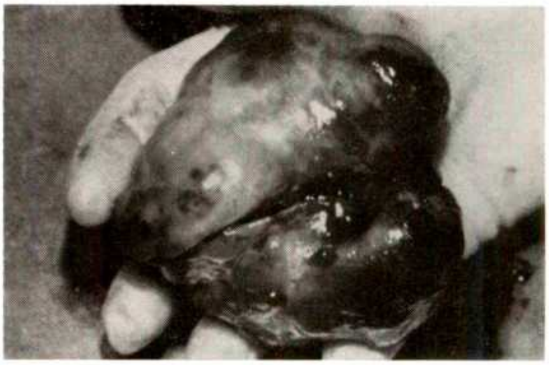

Fig. 2 *The appearance of the right atrial myxoma after surgical removal.*

Symptoms are said to be more variable when a tumour occurs in the right rather than the left atrium.[11] It was, however, a striking feature of this patient's history, that the symptoms were not only vague but also intermittent. Despite the presence of such a large tumour — one of the largest recorded[10 12]—she could be free from symptoms for several weeks. As symptoms were variable and often relieved by lying face down on a bed, it is possible that they were related to reductions in cardiac output produced by variable right atrial outflow obstruction.

Constitutional effects of atrial myxomata are common and include fever, anaemia, weight loss, increased sedimentation rate, and raised serum globulins.[12–14] Our patient had increased erythrocyte sedimentation rate and also increased alpha-2 and gamma globulins. It may be that her amenorrhoea, which lasted for five years and recovered after operation, was a result of a similar constitutional effect of the tumour. Though weakness and malaise have been described in other cases of right atrial myxoma, this patient's symptoms were present several years before when a consultant cardiologist had found no clinical, *x*-ray, or electrocardiographic abnormalitie.

To what extent her symptoms were initially caused by the tumour on the one hand or by her personality on the other, and whether her behaviour was entirely a result of a systemic effect of the tumour remain matters for speculation. Nevertheless, it seems that she now leads a normal life and her behaviour has been normal apart from initial anxiety about the possibility of recurrence of the tumour.

References

1 Sannerstedt R, Varnauskas E, Paulin S, Linder E, Ljunggren E, Werkö L. Right atrial myxoma. Report of a case and review of the literature. *Am Heart J* 1962; **64:** 243–54.

2 Morrisey JF, Campeti FL, Mahoney WB, Yu PN. Right atrial myxoma. *Am Heart J* 1963; **66:** 4–15.

3 Bahnson HT, Newman EV. Diagnosis and surgical removal of intracavitary myxoma of the right atrium. *Bull John Hopkins Hosp* 1953; **93:** 150–63.

4 Belle MS. Right atrial myxoma. *Circulation* 1959; **19:** 910–17.

5 Cooley DA, Norris GC Jr, Attar S. Cardiac myxoma. Surgical treatment in four cases. *Arch Surg* 1959; **78:** 410–17.

6 Ellis FH, Mankin HT, Burchell HB. Myxoma of the right atrium: successful surgical treatment in two cases. *Med Clin North Am* 1958; **42:** 1087–99.

7 Padhi RK, Kelly HG, Lynn RB. Intra-atrial myxoma. Review of literature and report of a right atrial myxoma diagnosed pre-operatively and successfully treated. *Can J Surg* 1959; **2:** 414–20.

8 Nasser WK, Davies RH, Dillon JC, *et al.* Atrial myoxoma. I. Clinical and pathological features in nine cases. *Am Heart J* 1972; **83:** 694–704.

9 Currey HLF, Mathews JA, Robinson J. Right atrial myxoma mimicking a rheumatic disorder. *Br Med J* 1967; **i:** 547–8.

10 Roguin N, Amikan S, Riss E. Prolapsing right atrial myxoma. Clinical and haemodynamic considerations. *Br Heart J* 1977; **39:** 577–80.

11 Bigelow JC, Herr RH, Starr A. Atrial myxoma. *Surgery* 1969; **65:** 247–55.

12 Goodwin JF. Diagnosis of left atrial myxoma. *Lancet* 1963; **i:** 464–8.

13 May IA, Kimball KG, Goldman PW, Dugan DJ. Left atrial myxoma—diagnosis, treatment and pre- and post-operative physiological studies. *J Thorac Cardiovas Surg* 1967; **53:** 805–13.

14 Goodwin JF. The spectrum of cardiac tumours. *Am J Cardiol* 1968; **21:** 307–14.

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Mycoplasma pneumoniae endocarditis

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SUMMARY We here describe a case of presumed *Mycoplasma pneumoniae* endocarditis complicating rheumatic aortic valvular disease. We do not know of any previously reported cases.

Since its identification by Chanock *et al.*[1] *Mycoplasma pneumoniae* (*M. pneumoniae*) has emerged as an important cause of upper and lower respiratory tract infections in man. However, this organism has been associated very rarely with disease of the cardiovascular system.[2] We report a case of presumed *M. pneumoniae* endocarditis in a patient with rheumatic heart disease; though pericarditis and myocarditis have been previously described, there are no reported cases of *M. pneumoniae* endocarditis.

Case reports

A 21-year-old Lebanese student was admitted with a four days' history of general malaise, lethargy, sore throat, and anorexia. He gave a past history of acute rheumatic fever with pancarditis in 1972 while in Kuwait. Four weeks before admission he had undergone dental extraction without appropriate antibiotic cover, though over the previous six years he had intermittently received long-acting benzyl-penicillin (Penidural) intramuscularly as prophylaxis against rheumatic fever. In addition, he had given himself opium intravenously on several occasions in the months before this illness.

Physical examination on admission revealed: fever (T=39·2°C) with rapid shallow breathing, sinus tachycardia, and a radial pulse of collapsing quality (blood pressure 140/40 mmHg). The apex beat was displaced outside the left mid-clavicular line with clinical features of left ventricular hypertrophy. On auscultation, there was a loud and long (grade 3/4) early diastolic murmur of aortic regurgitation, with mitral late systolic and mid-diastolic murmurs. Localised coarse crepitations were present at the right base posteriorly, suggesting pneumonitis. The spleen was enlarged and tender.

Investigation showed the following: haemoglobin 13·6 g/dl, white cell count 10 800/m^3 (67% neutrophils, 27% lymphocytes), and erythrocyte sedimentation rate 42 mm/h. Urine examination revealed microscopic haematuria and mild proteinuria. The electrocardiogram indicated left ventricular hypertrophy but also showed T wave inversion in limb leads III and aVF and praecordial leads V4 to V6. The chest *x*-ray film showed collapse and consolidation of the right lower lobe, a cardiothoracic ratio of 14:30, with slight enlargement of the ascending aorta and the configuration of left ventricular hypertrophy. An echocardiogram showed features consistent with severe aortic regurgitation but no vegetations were seen on the valves: the mitral valve was reported normal though there were diastolic vibrations. A left ventricular angiogram showed a dilated, vigorously contracting ventricle, with an ejection fraction of 0·61, and left ventricular end-diastolic pressure of 6 mmHg. The mean cardiac output (calculated from dye curves) was 5·46 l/min and the cardiac index 2·87 l/min per m^2. Aortic root injection revealed severe (grade 3) aortic regurgitation.

Very high and rising mycoplasma titres were present as shown in the Table. In addition, the IgM antibody titre was significantly raised (Mycoplasma Reference Laboratory, Norwich).

These values confirmed recent mycoplasma infection. Antibody titres for Q fever and routine blood cultures were negative. Cold agglutinins were not present but the serum haptoglobins were considerably reduced (0·2 g/l), suggesting recent haemolysis.

Table M. pneumoniae *antibody titres*

	On admission	*Seven days later*
(1) *M. pneumoniae* (complement fixation)	1:256	1:2048
(2) (IgM)	1:32	1:64

While awaiting results of blood culture and antibody titres intravenous treatment with 12 mega units of benzyl penicillin and gentamicin 240 mg daily was started and continued for six weeks. This was later followed by a four-week course of oxytetracycline. Considerable improvement followed the start of antibiotic treatment and the pyrexia subsided. However, aortic regurgitation worsened, and three months after presentation the patient underwent aortic valve replacement (with Carpentier Edwards xenograft). At operation, the aortic valve was found to be thickened and fibrotic, the aortic valve ring was dilated, and the aortic wall appeared normal. Microscopy of the valve cusp revealed organising thrombotic vegetations, though no micro-organisms were seen.

Discussion

Finkelstein and Klainer[3] were the first authors to describe the possible association of *M. pneumoniae* infection with cardiovascular disease, reporting three cases of pericarditis associated with clinical features of "atypical pneumonia". Since then, there have been a few single case reports of cardiovascular involvement with complications of pericarditis and perimyocarditis.[4 5] The largest survey was that of Sands *et al.*[6] who described, between 1970 and 1973, eight patients with acute pericarditis and five with perimyocarditis associated with *M. pneumoniae* infection.

Rising antibody titres against *M. pneumoniae* and the presence of specific IgM antibody provided strong evidence for a recent mycoplasma infection in our patient. That he also had active infective endocarditis was suggested by microscopical haematuria, the tender enlarged spleen, and the rapid disintegration of his aortic valve with vegetations seen on valve histology. The methods of routine blood culture used on his admission to hospital would not have grown the organism and subsequently the patient was given gentamicin followed by oxytetracycline, thereby negating special culture techniques, as gentamicin has recently been shown to be highly effective against mycoplasma species.

As a result of our experience, we therefore suggest that *M. pneumoniae* should be borne in mind as a possible source of infection when considering the cause of atypical infective endocarditis.

We acknowledge the help given by Dr R M Perinpanayagam, consultant microbiologist to Queen Mary's Hospital, and that of Mr M V Braimbridge, cardiothoracic surgeon to St Thomas's Hospital.

References

[1] Chanock RM, Hayflick L, Barile MF. Growth on artificial medium of an agent associated with atypical pneumonia and its identification as a PPLO. *Proc Nat Acad Sci USA* 1962; **48:** 41–9.
[2] Murray HW, Masur H, Senterfit LB, Roberts RB. The protean manifestations of *Mycoplasma pneumoniae* infections in adults. *Am J Med* 1975; **58:** 229–42.
[3] Finkelstein D, Klainer MJ. Pericarditis associated with primary atypical pneumonia. *Am Heart J* 1944; **28:** 385–94.
[4] Gerzén P, Granath A, Holmgren B, Zetterquist S. Acute myocarditis. A follow up study. *Br Heart J* 1972; **34:** 575–83.
[5] Lewes D, Rainford DJ, Lane WF. Symptomless myocarditis and myalgia in viral and *Mycoplasma pneumoniae* infections. *Br Heart J* 1974; **36:** 924–32.
[6] Sands MJ Jr, Salz JE, Turner ET Jr, Soloff LA. Pericarditis and Perimyocarditis associated with active *Mycoplasma pneumoniae* infection. *Ann Intern Med* 1977; **86:** 544–8.

Requests for reprints to Dr David Barnardo, Medical Unit, Queen Mary's Hospital, London SW15 5PN.

Correspondence

Br Heart J 1980; **44:** 113–5

Study of cardiac rhythm in healthy newborn infants

Sir,
The two papers by Southall and his colleagues[1 2] in a recent issue of *British Heart Journal* highlight the relative frequency of arrhythmias in neonates and children, but there are inaccuracies in the measurement and interpretation of several of the electrocardiograms which detract from the potential value of these papers.

In the first paper,[1] the measurement of the longest PP interval in Fig. 1, page 15, is incorrect. The length of this pause is approximately 1·16 s and not the 1580 ms quoted by the authors. Neither of these intervals is an exact, or nearly exact, multiple of the preceding or following PP intervals and the diagnosis of complete sinuatrial block is therefore difficult to support. Furthermore, the pause of 800 ms in Fig. 2, page 15, appears to be terminated by a P wave which is quite different in shape from the previous and subsequent P waves. Where such a pause is terminated by an escape beat from a lower pacemaker the rhythm is quite distinct from a 2:1 sinuatrial block. Though Southall *et al.*[1] have shown convincingly that sinus pauses are relatively common in neonates, they have not been precise in differentiating between the various forms of sinuatrial exit block and sinuatrial arrest.

In the second article,[2] the rhythm illustrated in Fig. 2, page 24, is described as probable ventricular tachycardia. The first six intervals of the figure are quite variable, ranging from approximately 0·2 to 0·4 s, and complexes 1 to 7 are relatively narrow. We were unable to discern any regular P wave pattern throughout this trace and we suggest that the basic rhythm is atrial fibrillation. The run of broad complexes (beats 8 to 12) with regular RR intervals are more typical of ventricular tachycardia, but the wide variation of RR intervals and QRS complex widths seen throughout this tracing is consistent with atrial fibrillation. In the lower panel of Fig. 4, page 25, the ventricular response rate is at its fastest 250 a minute, rather than the 300 a minute indicated in the authors' legend.

The same electrocardiogram is illustrated in both papers (Fig. 1, page 15; Fig. 3, page 25). We presume that a clerical or printing error led to this mistake But was this recorded from a healthy neonate or from a child with complete transposition?

Finally, we suggest that in epidemiological studies which make use of taped electrocardiography, a technique prone to artefact and error, very precise diagnosis should be avoided.[2] In this context abnormal sinus node function, such as sinus arrest and sinuatrial exit block, are best classified together as sinus pauses.

K Hellestrand, A J Camm,
Department of Cardiology,
St Bartholomew's Hospital,
London.

References

1 Southall DP, Richards J, Mitchell P, Brown DJ, Johnston PGB, Shinebourne EA. Study of cardiac rhythm in healthy newborn infants. *Br Heart J* 1980; **43:** 14–20.

2 Southall DP, Keeton BR, Leanage R, *et al.* Cardiac rhythm and conduction before and after Mustard's operation for complete transposition of the great arteries. *Br Heart J* 1980; **43:** 21–30.

This letter was shown to Dr Southall and his co-authors who reply as follows.

Sir,
We thank Drs Hellestrand and Camm for their constructive observations and for pointing out two clerical errors. Fig. 1 in paper 1 is misplaced and is correct as Fig. 3 in paper 2 (a preoperative recording on a 2-year-old child with transposition of the great arteries). We enclose the correct illustration for Fig. 1, paper 1 (Fig. A). The pause in Fig. 3, paper 2 should be 1180 not 1580 ms. We do not accept their opinion on our interpretation of

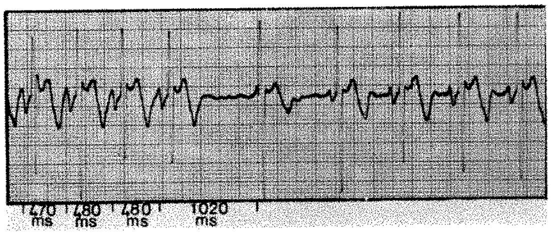

Fig. A

pauses on the electrocardiograms and suggest they have misunderstood this section of our paper.

A reliable diagnosis of sinuatrial exit block or sinus arrest can only be made by recording potentials directly from the sinus node. Though it has been stated[1–3] that measurement of atrial potentials, that is PP intervals on the surface electrocardiogram, may be used to diagnose exit block, such measurements may be complicated by other factors. Thus, in electrocardiographic patterns described as sinuatrial block exact whole multiples of PP intervals may be disturbed by autonomic effects or by escape pacemakers whose inherent rates are only slightly slower than the sinus pacemaker. In our paper it was not the intention precisely to define electrocardiographic patterns of exit block or sinus arrest. We simply measured PP or PQ intervals and categorised pauses arithmetically into groups. On the basis of this categorisation and considering the effects of autonomic tone and escape pacemaker activity, we contend that it is impossible to differentiate on the surface electrocardiogram the pauses we have described, from those previously described as sinuatrial exit block or sinus arrest.

Thus the PP or PQ intervals of the pauses in Fig. 3, paper 2, and the new Fig. A, paper 1, both exceed the immediately preceding PP interval by more than 110 per cent. We maintain that this pattern cannot be distinguished on the surface electrocardiogram from intermittent third degree sinuatrial exit block or sinus arrest. Distinction cannot be made between sinus arrest and complete exit block because sinus node potentials cannot be seen. Drs Hellestrand and Camm state that a distinction could be made on the basis of a mathematical relation between PP intervals, but we maintain that on the surface electrocardiogram this argument is incorrect because of possible variations in autonomic tone and the high intrinsic rate of escape pacemakers present in this age group.

In Fig. 2, paper 1, the heart rate preceding the pause is 150 per minute, and at this relatively high rate P wave configuration may be distorted by the preceding ventricular repolarisation and succeeding depolarisation. In addition, variation in P wave shape, which may be artefactual, is frequently present on 24-hour recordings. We agree that the P wave following this pause may represent an

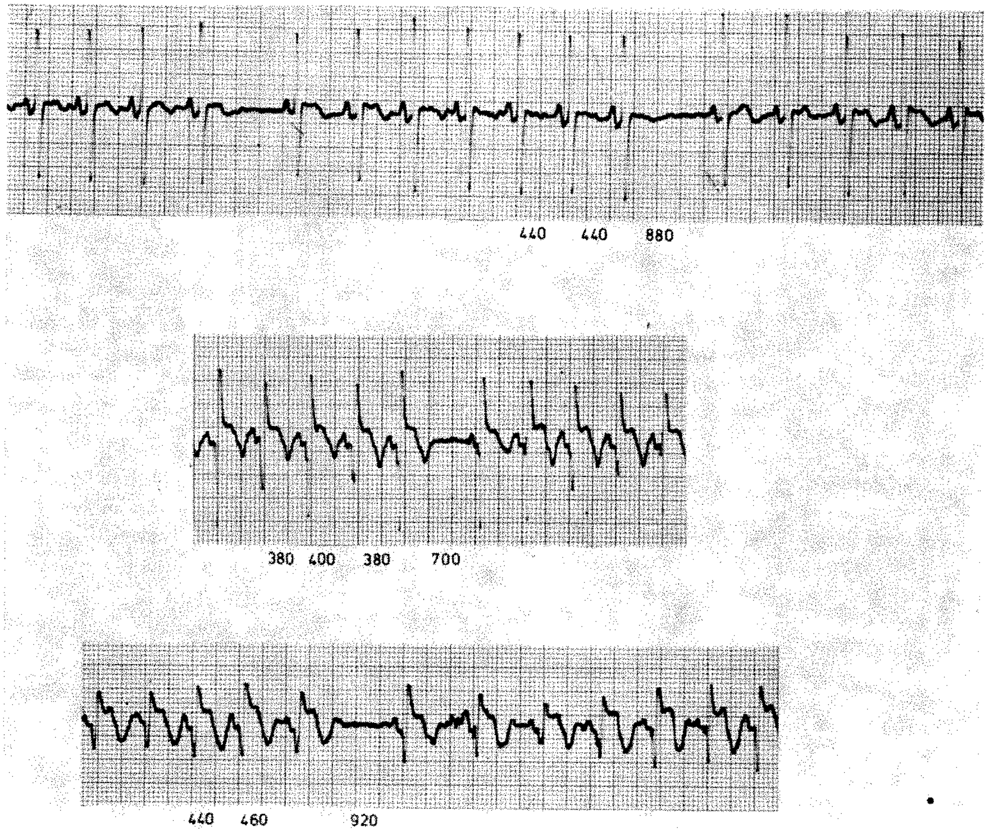

Fig. B

escape beat rather than an impulse of sinus origin and that this pattern is indistinguishable from the patterns of complete sinuatrial block or sinus arrest with a P wave fortuitously occurring at between 190 and 210 per cent of the previous PP interval. We enclose further examples of such pauses (Fig. B) which illustrate the difficulty of distinguishing between patterns of sinuatrial block and patterns of sinus arrest terminated by atrial or junctional escape beats. This impasse was a further reason for using arithmetical measurements of PP or PQ intervals for defining categories of pause rather than using established definititions with their emotive connotations.

We agree that the electrocardiographic trace in Fig. 2, paper 2, does not show regular P wave activity. The absence of regular P waves, however, cannot be taken as definitive evidence for atrial fibrillation, though this diagnosis is possible. We contend that the presence of broad complexes (beats 8 to 12) with regular RR intervals comprising the tachycardia and ventricular premature beats during sinus rhythm in the remainder of the 24-hour recording suggests that this electrocardiographic trace is more likely to represent ventricular tachycardia. We agree that in Fig. 4, paper 2, the fastest ventricular rate is 270 a minute for three complexes and 250 a minute for nine complexes.

Finally, we agree that the term "sinus pause" is appropriate for describing sudden PP interval prolongation and, in fact, used this term in our summary to paper 1. We maintain that some of these PP interval patterns cannot be distinguished on the surface electrocardiogram from those described as exit block or sinus arrest. Such patterns have been said to represent abnormal sinus node function but their high incidence in healthy infants and children strongly suggests that they are normal findings and that other electrocardiographic criteria are required to define abnormal sinus node function.

D P Southall, E A Shinebourne,
Cardiothoracic Institute,
London.

References

1 Myerburg RJ. Electrocardiographic diagnosis of sinus node rhythm variations and SA block. In: Schlant RE, Willis-Hurst J, eds. *Advances in electrocardiography.* New York: Grune & Stratton, 1972: 73–80.

2 Stock JPP, Williams DO. *Diagnosis and treatment of cardiac arrhythmias.* 3rd ed. London: Butterworth, 1974: 224–65.

3 Schamroth L. *The disorders of cardiac rhythm.* Oxford and Edinburgh: Blackwell Scientific Publications, 1971: 193–6.

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12th International Congress of Chemotherapy

This will take place on 19 to 24 July 1981 in Florence, Italy. Deadline for abstracts: 15 February 1981. For further information write to: Secretariat, 12th International Congress of Chemotherapy, Via della Scala 10, Florence, Italy, 50123—Florence.

International Conference on Computers

The seventh annual international conference on computers in cardiology will be held on 21 to 24 October 1980 in Williamsburg, Virginia, USA.

Correspondence regarding registration and conference accommodations should be directed to: Computers in Cardiology, PO Box 639, Silver Spring, Maryland 20901, USA.

Association of Thoracic and Cardiovascular Surgeons of Asia

The Fifth Congress of the Association of Thoracic and Cardiovascular Surgeons of Asia will be held at Hotel Taj Coromandel, Madras, from 14 to 18 February 1981.

For further details write to: Dr Solomon Victor, Secretary, Vth Congress ATCVSA, 15 East Street, Kilpauk Garden Colony, Madras-600010, India

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Dr Edgar Haber, Head of the Department of Cardiology, Massachusetts General Hospital, Boston, USA, will be the first International Lecturer of the ISFC. He will give the International Lecture on "immunological probes in cardiovascular disease" at the Royal College of Physicians, London, at 6.00pm on 4 December 1980, under the chairmanship of Sir Douglas Black, President, Royal College of Physicians.

Dr Haber will also deliver an ISFC lecture (sponsored by May & Baker Limited) in Edinburgh, under the auspices of the Department of Cardiology, University of Edinburgh; an ISFC lecture (sponsored by May & Baker Limited) in Glasgow, under the auspices of the Department of Cardiology, University of Glasgow.

Details will be published in due course, and may be obtained from: Madame Marianne de Figueiredo, Central Office, International Society and Federation of Cardiology, PO Box 117, CH-1211 Geneva 12 (Switzerland).

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This will take place in Florence, Italy, 4 to 6 May 1981, and is organised by the European Working Group on Cardiac Pacing in co-operation with the Italian Pacing Association.

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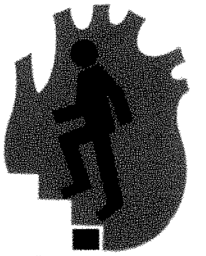

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References
1. Nayler, W.G. *Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
2. Flameng, W. *et al. Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
3. Detry, J.M.R. *et al. Eur. J. Cardiol.* **4,** 165, 1976.
4. Gobel, F.L. *et al. Am. J. Cardiol.* **37,** 139, 1976.
5. Jenkins, M.D. *et al. Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
6. Bloem, Th. J.J.M. *et al. Clin. Cardiol.* **2,** 407, 1979.
7. Shapiro, W. *Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
8. Nordstrom, L.A. *Chest*, **74,** 50, 1978.

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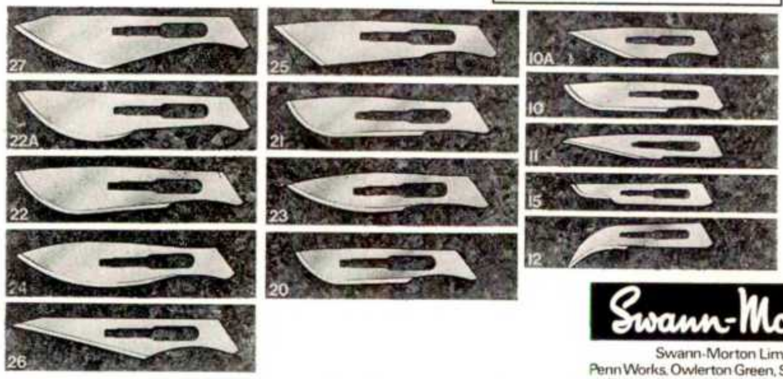

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Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41:** 263–7.

(2) *Books and other monographs:*
Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977*. Edinburgh, London: Churchill Livingstone, 1978: 16–26.

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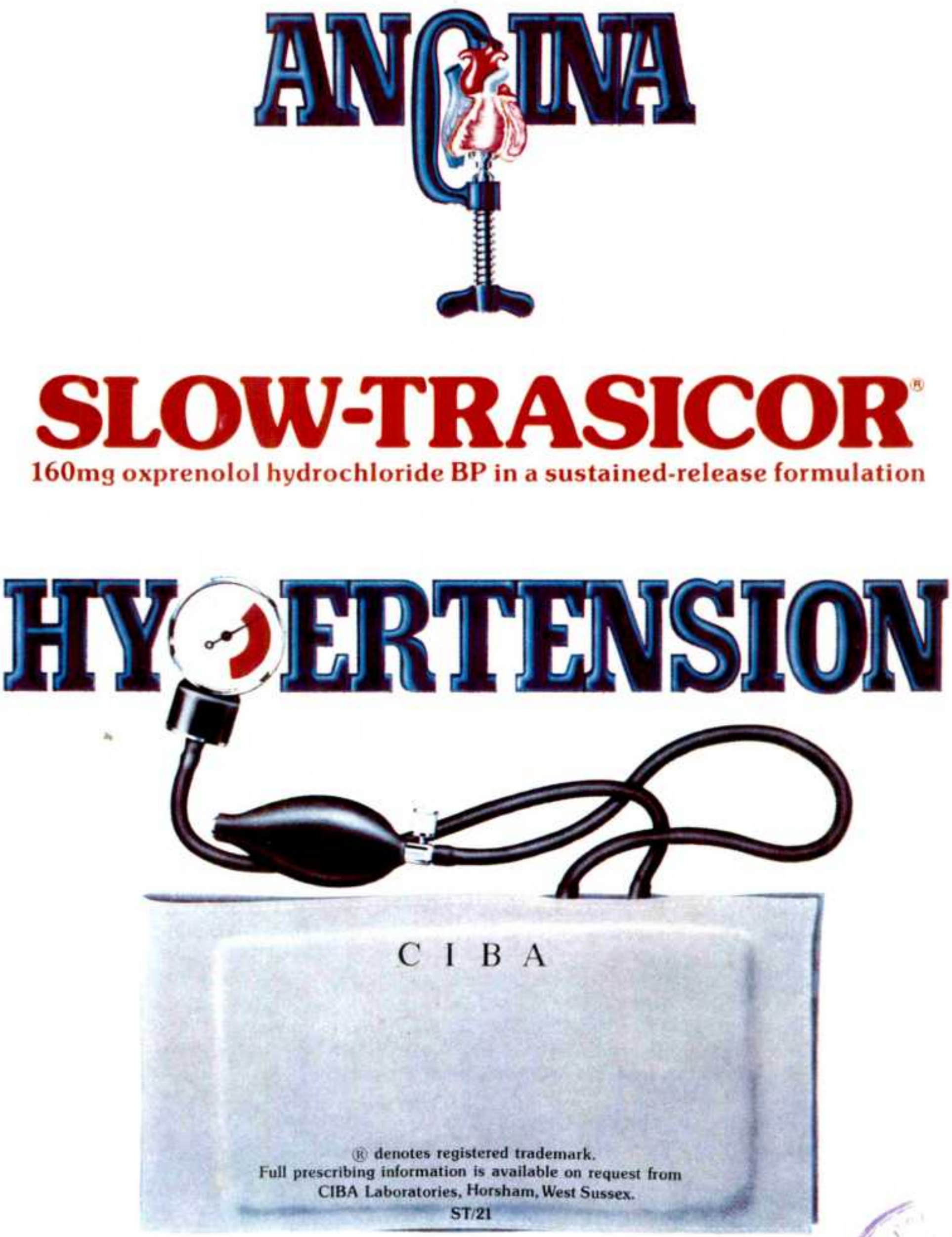

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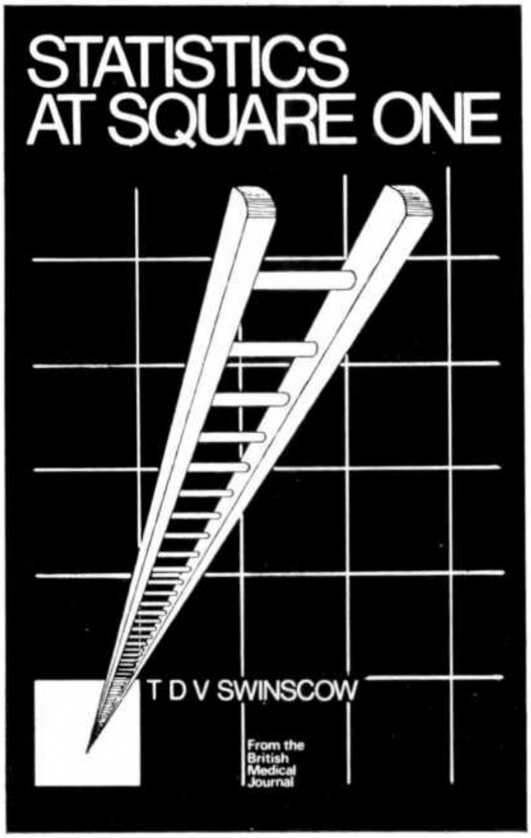

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Beneficial effects of long-term beta-blockade in congestive cardiomyopathy

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SUMMARY Twenty-eight patients with heart failure caused by congestive cardiomyopathy, which had been diagnosed according to the criteria of Goodwin and Oakley, were treated with beta-blocking agents for six to 62 months, except for four patients who died within two months. Repeated non-invasive investigations were performed before and during treatment as well as exercise tests and chest x-rays. The echocardiographic and pulse curve findings indicated an improvement in systolic and diastolic myocardial function. The ejection fraction increased from $0{\cdot}32 \pm 0{\cdot}02$ to $0{\cdot}42 \pm 0{\cdot}04$, and the third heart sound amplitude and rapid filling wave were significantly reduced. The functional classification improved in 15 patients while in 12 patients it remained unchanged and in one it deteriorated. During follow-up, 10 patients died, most of them suddenly. The mortality was lower than expected in this severely ill group of patients.

The beneficial effect of chronic beta-blockade in patients with congestive cardiomyopathy suggests that catecholamines are involved in the pathogenesis of congestive cardiomyopathy, and that patients with congestive cardiomyopathy may have inappropriate sympathetic cardiac stimulation which can be reduced by chronic beta-blockade. It is suggested that beta-receptor blockade should be added to conventional treatment with digitalis and diuretics in all patients with severe myocardial failure caused by congestive cardiomyopathy.

Patients with congestive cardiomyopathy (COCM) are usually treated with digitalis and diuretics for relief of heart failure. The prognosis is considered poor when heart failure is severe despite optimal conventional treatment.[1–4] Temporary improvement of heart failure has been reported after very long periods of bed rest.[5] In 1975 Waagstein *et al.*[6] reported from this clinic that seven patients with COCM and heart failure showed improved myocardial function and exercise capacity on chronic beta-receptor blockade.

This study was undertaken to evaluate further the effects of beta-blockade in patients with COCM. Twenty-eight patients were treated with beta-blocking agents for six to 62 months, except four patients who died within two months. Their myocardial function was assessed before the start of treatment and repeatedly thereafter by standard non-invasive investigations at the department of clinical physiology including echocardiography and pulse curves. Since repeated assessment of cardiac function was planned in this study, invasive investigations were judged unethical. Cardiac catheterisation was performed in only four of the early patients enrolled in the study. Coronary angiography was performed in 14 other patients, in each case without pathological findings. None of the patients included in this study had a history of coronary artery disease.

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Patients

Twenty-eight patients (21 men and seven women, aged 16 to 60 years, mean age 46 years) were included in the study. All were diagnosed as having COCM according to the criteria proposed by Goodwin and Oakley,[7] that is a heart muscle disorder with depressed systolic function without known cause. Patients were not included if there was a history of coronary artery disease or abnormal coronary angiography; none had a history of alcohol abuse or systemic disease. All patients gave a history of dyspnoea, its duration varying from three to 172 months (median value 12 months), despite treatment with digitalis and diuretics. The details of patients are summarised in Table 1. Twenty-seven of the patients entered an observation period of at least one month, with the dosage of digitalis and diuretics unchanged before starting beta-blockade or placebo treatment. One patient, a 16-year-old girl (case 20), deteriorated during the first two weeks of observation and a beta-blocker was given because of concern for her condition. The first eight patients started on beta-blockade immediately after the observation period and then were followed up regularly. Five of these patients were included in our previous paper.[6] For the remaining 20 patients (cases 9 to 28) the intention was, after the initial observation period, to give all of them single-blind placebo treatment for three months before starting beta-blockade. However, this plan could only be followed in 16 patients. Four patients (cases 17, 20, 24, and 27), because their condition was considered to be life-threatening, were given beta-blockers as above and no placebo. The procedure allowed the placebo period to be prolonged if, during it, signs of haemodynamic improvement could be seen, as judged by the non-invasive investigations mentioned above. In 11 of the 16 patients, placebo treatment was continued for three months. Two patients (cases 11 and 16) were given beta-blockers before the end of this three-month period, because of severe deterioration in their condition, and three others continued on placebo for six months to enable one to assess the stability of theirs.

BETA-BLOCKER TREATMENT

In six of the seven patients first treated with beta blockers the cardioselective agent practolol was used. It was thought on theoretical grounds that a cardioselective drug, with less influence on peripheral vascular resistance, should have advantages over non-selective beta-blockers, with their attendant risk of unmasking alpha-receptor-induced vasoconstriction. However, one of the first patients was treated with the non-selective agent alprenolol, which produced the same response as practolol did in the others. After this observation, alprenolol was given to the next nine patients enrolled in the study in doses varying between 25 mg three times daily and 100 mg twice a day. Because of difficulties experienced in increasing the alprenolol dose, and also because there were three early deaths (cases 9, 11, and 12) in this group, all patients were changed

Table 1 *Patients with congestive cardiomyopathy treated with chronic beta blockade as well as digitalis and diuretics*

Case no.	*Sex*	*Age (y)*	*Symptom duration (mth)*	*Placebo (mth)*	*Treatment (mth)*	*Outcome 1 April 1978*	*Beta-blockade*	
							Initial drug	*Present/last drug/dose*
1	M	55	15	—	50		P	A 100 mg×2
2	M	46	80	—	12	Death	P	P 100 mg×2
3	F	33	12	—	54		P	A 25 mg×3
4	F	58	57	—	62		A	M 25 mg×2
5	M	59	46	—	30	Death	P	M 50 mg×3
6	M	50	23	—	47		P	M 50 mg×3
7	M	60	12	—	25	Death	P	P 100 mg×2
8	M	56	7	—	42	Death	P	M 50 mg×2
9	M	59	64	3	1·5	Death	A	A 25 mg×2
10	M	46	10	3	37		A	M 25 mg×2
11	F	60	42	1	1·5	Death	A	A 25 mg×2
12	M	46	13	3	2	Death	A	A 50 mg×3
13	M	56	21	3	37		A	M 50 mg×2
14	M	59	24	3	32		A	M 50 mg×3
15	F	60	11	3	32		A	PR 40 mg×3
16	M	58	160	2	31	Death	A	M 25 mg×2
17	M	16	4	0	32		M	M 50 mg×3
18	M	34	15	3	10		M	A 100 mg×2
19	M	49	8	3	22		M	PR 40 mg×2
20	F	16	3	0	22		M	M 50 mg×2
21	M	52	172	3	10	Death	M	A 25 mg×3
22	M	50	14	6	17		M	M 50 mg×2
23	F	22	19	6	18		M	M 50 mg×3
24	F	48	10	0	0·75	Death	M	M 50 mg×3
25	M	56	18	6	7		M	M 50 mg×2
26	M	18	6	3	7		M	M 25 mg×2
27	M	25	24	0	6		M	M 100 mg×2
28	M	50	6	3	6		M	M 25 mg×2

A, alprenolol; M, metoprolol; P, practolol; PR, propranolol.
Symptom duration is until start of treatment with beta-blockade or placebo.

from alprenolol to metoprolol treatment within six months. With great differences in response between patients, difficulties were anticipated in the evaluation of the importance of cardioselectivity and the last 12 patients included in the study all received metoprolol from the start of treatment. The usual initial dose of metoprolol was 25 mg a day which could be increased by 25 mg each day or every second day. In three patients (cases 17, 20, and 28) whose clinical condition was extremely poor, the initial dose was 12·5 mg a day and it was increased slowly, by 12·5 to 25 mg every second or third day. Systolic blood pressure and resting heart rate were measured five to six times a day, the aim of treatment being a blood pressure above 100 mmHg and a heart rate of 70 beats per minute. The duration of beta-blocker treatment, the initial drug used, and the final drug and dosage are given in Table 1 for all of the patients.

Methods

NON-INVASIVE INVESTIGATIONS

Investigations were performed according to a standard procedure in all patients, usually at the same time each day. Because it was possible to perform these investigations on several occasions during the follow-up period, myocardial function could be repeatedly assessed. Investigations included phonocardiograms from five standard areas, an apex cardiogram, pulse tracings from the carotid artery, jugular vein, and liver, and an echocardiogram. All records, with the exception of the echocardiogram, were made using an eight-channel ink-recorder (Mingograph 81, Elema-Schönander) at a paper speed of 100 mm/s. The phonocardiograms were recorded with an acceleration microphone (Elema-Schönander EMT 25C) fixed to the thoracic wall with adhesive tape. The amplitude of the third and fourth heart sounds was measured from the apical recording in the 25 or 50 Hz band with an amplification of 1/10, using the mean value of three beats. The apex cardiogram and the pulse tracings were all performed with a hand-held funnel-shaped pick-up, internal diameter 2·5 cm, connected to a crystal transducer (Elema-Schönander EMT 510C) by a 35 cm latex tube. This combined system had a time constant of 1·9 to 4·6 seconds (depending on the individual amplification used for each curve) and a frequency response of at least 0·08 (at a time constant of 1·9 seconds) to 65 Hz.[8] Left ventricular ejection time was measured from the carotid pulse and corrected for heart rate according to the method of Meiners.[9 10] This technique expresses left ventricular ejection time as a percentage of the normal left ventricular ejection time for the actual heart rate. The apex cardiogram was recorded with the patient in the left lateral position. The "a" wave and the rapid filling wave (RFW) were expressed as a percentage of the total amplitude of the pulse curve (H). All measurements were calculated as the mean of values from at least three cardiac cycles.

A commercially available ultrasonoscope (Ekoscan 30, Mediscan) was employed for echocardiography, using a 2·25 MHz transducer, with 10 cm focus and a repetition rate of 1000 impulses/second. Before 1975, polaroid photographs of the time motion display were taken from a slave storage oscilloscope (Textronix 603). From 1975 a fibreoptic recorder was used in all investigations (Honeywell Visicorder 1856).

Stroke volume was calculated from the end-diastolic and end-systolic volumes, derived by the cube method,[11] and the ejection factor (EF) from the stroke volume and end-diastolic volume. The mean velocity of circumferential fibre shortening (mean V_{CF}) was calculated according to the method of Cooper *et al.*,[12] except that left ventricular ejection time in the formula was derived from the carotid pulse curve.

All data were summarised in a report which included both the diagnosis and an evaluation of the severity of myocardial dysfunction. The diagnosis of congestive cardiomyopathy was based on the finding of a dilated left ventricle with symmetrically depressed systolic function, without hypokinetic areas to suggest coronary artery disease. The severity was assessed by a combination of direct measurements of pump function (EF and mean V_{CF}), and indirect evidence of forward and backward failure.

The principles used in assessing the degree of myocardial dysfunction are based on earlier experience and are described below. In mild to moderately severe myocardial dysfunction, with left ventricular end-diastolic diameter (LVEDD) around 5·5 to 7·0 cm, EF 0·40 to 0·60, and mean V_{CF} 0·70 to 1·00, pump function seems to be adequate, at least at rest, and there are often no signs of disturbed diastolic function. In more severe cases of congestive cardiomyopathy with LVEDD between 7 and 10 cm, EF $<$ 0·40, and mean $V_{CF} < 0{\cdot}70$, diastolic function is also disturbed to a varying degree. At this stage, signs of decreased distensibility and backward failure occur. When the left ventricle is resistant to filling because of wall and/or volume stiffness, the most important compensatory mechanism is a strengthening of atrial contraction producing an increased atrial contribution to diastolic inflow. This increased atrial contraction produces a pathological fourth heart sound and an a/H ratio > 15 per cent, and a moderate enlargement of the left atrial anteroposterior diameter frequently occurs. In most cases of severe COCM, however, this compensatory increase in atrial contraction is not sufficient to create an adequate stroke volume. With decreasing stroke volume, the left ventricular ejection time falls below 90 per cent. If cardiac output then becomes inadequate, signs of stasis and backward failure appear as a third heart sound, a pathological rapid filling wave in the apex cardiogram, a reinforced pulmonary component of the second heart sound, and, sometimes, dilatation of the right heart with signs of tricuspid regurgitation in the jugular and hepatic tracings. At each level of decompensation complementary findings are seen by the different techniques and the degree of decompensation can thus be established by several criteria. For example, the pulmonary and tricuspid valve movements usually change in pulmonary hypertension and the mitral valve motion mirrors different degrees of obstruction to ventricular filling, supporting the evidence of the diastolic extra sounds and the shape changes of the apex curve. With a severe degree of backward failure the left atrium dilates further, but, as the contractile force usually diminishes, the fourth heart sound and the a/H ratio may return to normal. This is in these cases a pathological change. In contrast, if myocardial function improves, with less distension of the left atrium, pathological values may reappear.

When the left ventricle is severely dilated with an LVEDD of about 8 to 10 cm, secondary mitral regurgitation usually occurs. Since the resistance to ventricular emptying then falls because of regurgitation into the left atrium, this can result in an increase in the EF and mean V_{CF}, giving a false impression of improved systolic myocardial function. Changing degrees of mitral regurgitation are a real problem in the evaluation both of different patients and in the longitudinal follow-up of single individuals. If, for example, the patients respond to treatment and the degree of mitral regurgitation decreases or disappears, the EF and mean V_{CF} may decrease giving the impression of deteriorating myocardial function. The EF and mean V_{CF} can therefore be misleading if used in isolation and must be complemented by measurement of LVET and the whole battery of signs of backward failure to be properly interpreted in cases of severe cardiomyopathy.

EXERCISE TESTS

Dynamic exercise was performed seated, using an electromagnetically braked bicycle (Siemens-Elema AB). The workload was increased by 20 watts every two minutes until exhaustion or haemodynamically important arrhythmias developed. The electrocardiogram was recorded continuously through chest-head leads. Blood pressure was measured by the cuff method. Work-pulse was calculated according to the equation:

$$\frac{\text{Workload (watt)} \times 60}{\text{Heart rate/minute}} = \text{joules/beat}$$

INVASIVE INVESTIGATIONS

Only four of the patients (cases 1, 2, 6, and 7) were catheterised as part of the clinical evaluation before and during beta-blockade. As repeated investigations were planned, non-invasive techniques were used thereafter. Catheterisations were performed at rest in the supine position without premedication. Pulmonary pressures were recorded by a Cournand catheter and arterial pressures by a polyethylene catheter in the brachial artery. Pressures were recorded through Statham 23 Db transducers and Honeywell amplifiers and registered on ultraviolet paper. The reference level was 5 cm below the sternum. Cardiac output was determined by the direct Fick principle or by the indicator dilution technique. Selective coronary and left ventricular angiograms were performed in 14 of the older patients and all coronary angiograms were normal.

STATISTICS

Comparison before and during treatment has been made with Student's t test for paired observations. In the text the mean values ±SEM are given.

Results

CLINICAL FINDINGS

Twenty-eight patients were studied before treatment, and with up to 62 months of chronic beta blockade. As can be seen from Table 1, the duration of symptoms before treatment varied from three to 172 months. The treatment period equalled or exceeded six months in 24 patients, and was shorter than this in four patients who died early. In all patients, a low dose of a beta-blocking agent was given initially because of the risk of inducing heart failure. The maintenance doses used are shown in Table 1.

From Table 2 it can be seen that, in terms of functional group, 15 patients improved, 12 were unchanged, and one patient deteriorated. The improvement seen was not related to the patients' initial functional group nor to the duration of pretreatment symptoms. A very pronounced improvement occurred in cases 1, 4, 10, 16, 17, 20, and 22,

Table 2 *Functional grouping according to New York Heart Association criteria before and during treatment with beta-blockers*

Case no.	*Functional group*	*Months after start of beta-blockade*						
		1	*3*	*6*	*12*	*18*	*24*	*36*
1	IV	III	III	III	II	II	II	II
2	III	III	III	III	†			
3	III	III	III	III	III	III	III	III
4	III	III	III	II	II	II	II	II
5	IV	III	III	III	III	III	III	†
6	III	III	III	III	III	III	IV	III
7	III	III	III	III	III	III	III	†
8	III	III	III	III	II	II	III	III
9	III	III	†					
10	III	IV	II	II	I	I	I	II
11	IV	†						
12	III	III	†					
13	III	III	III	II	II	II	II	II
14	III	III	III	II	II	II	II	II
15	III	III	III	III	III	III	III	III
16	IV	III	III	III	II	II	II	†
17	IV	III	II	II	II	II	I	
18	III	III	III	III	III			
19	III	III	III	III	III	III		
20	IV	III	II	I	I	I		
21	III	III	III	III	†			
22	III	III	II	II	I	I		
23	II	II	I	I				
24	III	†						
25	III	III	III	III				
26	III	III	III	II				
27	IV	II	II	II				
28	IV	III	III	III				

† = dead.

and five of these returned to full-time work (cases 10, 16, 17, 20, and 22). Three of the patients showed a dramatic improvement (cases 1, 17, and 20) in their clinical condition, and two of those (cases 17 and 20) are described in detail in the case reports while case 1 is described elsewhere.[13]

During the follow-up period 10 patients died, seven of them without showing clinical deterioration after the start of beta-blockade (cases 2, 7, 8, 9, 12, 21, and 24; Table 2). Two patients died after their clinical condition had improved as a result of more than two years' treatment (cases 5 and 16). One patient deteriorated gradually after the start of beta-blockade, treatment was discontinued after five weeks, and she died one week later (case 11). In none of the other nine patients was the addition of beta-blockade to their conventional treatment considered to have increased their cardiac decompensation. Seven of the patients died suddenly and three died from cardiac decompensation. Four of the 10 patients died within three months of starting beta-blockade, and three of these died suddenly (cases 10, 12, and 24).

Case reports

The clinical course is illustrated by the following three cases.

CASE 17

This was a 16-year-old boy who developed a throat infection in March 1975. He recovered in a week but 10 days later he again became febrile and a chest *x*-ray showed cardiomegaly (800 ml/m^2) and bronchopneumonia. He was treated with digoxin and frusemide at another centre for one month. Repeated blood cultures were negative and his fever disappeared in a few days. The patient's clinical condition remained unchanged during the first month as did his cardiac enlargement. He was readmitted to the hospital three-and-a-half months after the first admission, giving a one-week history of increasing exertional dyspnoea and gastrointestinal discomfort. He was referred to our hospital 10 days later, four months after cardiomegaly was first noted. On admission he was breathless at rest. Auscultation showed a third heart sound, gallop rhythm, and an apical systolic murmur. The blood pressure was 110/80 mmHg and the heart rate 120 beats/min. Investigations (Table 3) gave the following results: LVEDD 8·3 cm, EF 0·16, LVET 73 per cent, a loud third heart sound, and much increased rapid filling wave ratio. Cardiac volume was 950 ml/m^2. Over the following week his condition deteriorated with increasing dyspnoea, peripheral cyanosis, and hypotension, and treatment with metoprolol 10 mg three times a day orally was started in addition to the digoxin and frusemide. Over the following days, his heart rate decreased from 110 beats/min to 85 to 90 beats/min and the blood pressure increased to 110/90 mmHg. However, nocturnal dyspnoea persisted during this time. During the second week, the metoprolol dose was slowly increased to 25 mg three times a day, and the patient's clinical condition improved gradually thereafter, with reduced dyspnoea. After seven weeks he was taking 125 mg a day of metoprolol and investigations indicated a slight improvement, with EF 0·25 and diminished extra sounds but unchanged LVEDD of 8·2 cm. Over the following months, the patient was able to resume work at his father's farm. Repeated investigations six months later showed a further improvement in myocardial function. The LVEDD had decreased to 7·5 cm, and the EF was 0·37. The LVET was 85 per cent and there were faint extra sounds but the apical systolic murmur remained. The cardiac volume at this time was 650 ml/m^2. The patient was able to work to up to 160 watts on a bicycle ergometer. This improvement continued and one year after the start of beta-blockade the patient was in full-time work at the farm. A further investigation two-and-a-half years after the start of treatment (Table 3) disclosed an LVEDD of 8·2 cm, an EF

Table 3 *Results from first non-invasive investigation before (C), and last investigations during (B) beta-blockade in 28 patients with congestive cardiomyopathy*

Case no.	*LVEDD (cm)*		*EF*		*Mean V_{CF} (circ/s)*		*LA size (cm)*		*LVET (%)*		*3rd heart sound (mm)*		*4th heart sound (mm)*	
	C	*B*	*C*	*B*	*C*	*B*	*C*	*B*	*C*	*B*	*C*	*B*	*C*	*B*
1	6·2	4·8	0·21	0·68	?	0·56	4·5	4·5	75	88	21	2	23	0
2	6·7	5·6	?	?	?	?	5·0	4·3	70	77	28	2	F	F
3	8·4	9·7	0·29	0·35	?	0·72	3·9	4·6	80	90	0	2	3	0
4	7·0	5·7	?	0·65	?	1·15	5·0	3·9	85	95	19	0	3	2
5	—	6·8	—	0·35	—	?	—	5·3	—	80	—	2	—	0
6	8·0	10·0	?	0·32	?	0·44	5·0	5·0	87	93	?	0	11	2
7	9·0	8·2	0·29	0·63	0·63	?	4·9	?	67	80	20	4	?	0
8	6·4	8·2	?	?	?	?	4·8	5·0	90	100	3	3	0	3
9	9·0	—	0·18	—	0·41	—	5·2	—	83	—	3	—	F	—
10	6·7	7·1	0·46	0·46	0·80	0·83	4·9	4·8	85	88	6	2	F	F
11	7·1	—	0·28	—	0·45	—	3·9	—	95	—	6	—	3	—
12	7·3	—	0·23	—	0·40	—	4·5	—	83	—	3	—	3	—
13	8·0	7·2	0·24	0·58	0·36	0·55	4·8	5·0	87	95	0	0	1	0
14	6·1	6·1	0·31	0·52	0·56	0·77	4·3	4·6	80	80	12	5	F	F
15	6·0	6·0	0·49	0·65	0·67	0·95	4·4	4·0	100	105	2	2	4	1
16	6·8	6·9	0·54	0·54	1·12	0·76	5·8	6·0	72	85	9	4	F	F
17	8·3	8·2	0·16	0·50	0·27	0·69	4·2	3 8	73	90	5	0	8	3
18	6 6	7·0	0·48	0·40	0·87	0·52	5·2	3·0	83	82	8	21	9	2
19	7·2	7·4	0·45	0·40	0·50	0·56	5·6	5·8	84	90	6	2	2	0
20	7·0	5·2	0·42	0·53	0·74	0·80	4·3	3·3	85	95	39	2	?	0
21	8·0	7·0	0·25	0·31	0·60	0·50	5·4	6·8	88	77	6	12	F	F
22	7·3	6·7	0·32	0·50	0·49	0·80	3·8	4·0	88	90	4	0	0	0
23	6·6	6·3	0·34	0·56	0·48	0·85	3·4	3·1	86	90	0	0	0	0
24	7·4	—	0·30	—	0·87	—	5·5	—	66	—	10	—	3	—
25	9·2	8·9	0·33	0·40	0·54	0·61	5·2	4·4	83	90	9	1	7	3
26	7·1	7·2	0·35	0·36	0·60	0·53	5·5	6·0	88	95	6	0	24	4
27	8·0	7·4	0·36	0·27	0·54	0·47	7·0	7·4	95	85	12	27	0	4
28	8·0	7·2	0·26	0·48	0·54	0·83	4·4	5·8	70	73	0	0	10	3

LVEDD, left ventricular end-diastolic diameter; EF, ejection fraction; LA, left atrium; LVET, left ventricular ejection time; RFW, rapid filling wave.

of 0·50, and LVET of 90 per cent, a faint third heart sound, and an apical systolic murmur. The patient had a normal working capacity.

CASE 20

This was a 17-year-old girl who had had bronchial asthma since childhood. Despite this, she had worked as a groom for 10 months, and was receiving treatment with terbutaline by inhalation. For three months before admission, she had suffered from increasing exertional dyspnoea, and for the last month from epigastric discomfort. On admission in May 1976 she was dyspnoeic but without peripheral oedema or pulmonary râles. There was significant hepatic enlargement. On auscultation a third heart sound and a weak apical systolic murmur could be heard. The heart rate was 140 beats/min (LVEDD 7·1 cm, EF 0·35, LVET 55%). Treatment with digoxin and frusemide was started. Five days later the patient's condition had improved but she was still in functional group IV. Investigations (Fig. 1; Table 3) showed an LVEDD of 7·0 cm, an EF of 0·42, an LVET of 85 per cent, and a loud third heart sound, an increased RFW/H ratio, and a weak mitral regurgitation murmur. One week later her condition was unchanged. Cardiac catheterisation showed an arterial pressure of 80/57 mmHg, a pulmonary artery pressure of 42/26 mmHg, and a wedge pressure of 27 mmHg. The cardiac index was 1·7 l/min per m^2 and the stroke index 17 ml/m^2. After metoprolol 10 mg intravenously, cardiac output decreased acutely from 2·7 to 2·1 litres while pressure recordings were essentially unchanged.

Treatment with metoprolol 12·5 mg orally three times a day was started, the dose being increased to 125 mg daily within two weeks as her clinical condition improved. The heart rate was 100 to 110 beats/min during this period. Repeated investigations showed a much reduced third heart sound but otherwise unchanged results. During the next month there was a steady improvement in her condition, with diminished dyspnoea and heart rate and an increased blood pressure. Frusemide was withdrawn. Two months after the start of beta blockade the patient could manage ordinary activities without distress. Investigations at this time showed an LVEDD of 6·4 cm, an EF of 0·48, a much reduced third heart sound and RFW/H ratio, and no apical murmur. One month later she was free of exertional dyspnoea and resumed work. Her asthma was controlled without difficulty on

RFW/H ratio (%)		*a/H ratio* (%)		*Mitral regurgitation*		
C	*B*	*C*	*B*	*C*	*B*	
17	10	10	10	Yes	No	
19	0	F	F	Yes	No	
18	6	26	14	Yes	Yes	
37	4	10	10	No	No	
—	9	—	12	No	—	(Not investigated before)
39	0	53	18	?	No	
14	5	?	?	Yes	Yes	
11	4	32	34	Yes	Yes	
13	—	F	—	Yes	—	(Died)
15	3	F	F	No	No	
16	—	30	—	Yes	—	(Died)
16	—	48	—	No	—	(Died)
—	—	—	—	No	No	(Apex curve not obtained)
12	2	F	F	No	No	
8	8	14	12	No	No	
15	2	F	F	Yes	Yes	
16	0	33	11	Yes	Yes	
10	8	20	20	Yes	Yes	
13	6	14	23	Yes	No	
33	16	23	5	Yes	No	
30	31	F	F	Yes	Yes	
8	0	8	0	No	No	
10	0	18	4	Yes	No	
11	—	22	—	No	—	(Died)
10	0	14	10	Yes	Yes	
34	24	23	28	Yes	Yes	
49	58	18	26	Yes	Yes	
18	7	45	29	Yes	Yes	

three daily puffs of terbutaline, while she was taking metoprolol 50 mg twice daily. One-and-a-half years later she was considered to be in functional group I. Investigation at this time (Fig. 2; Table 3) showed an almost normal systolic myocardial function with an LVEDD of 5·2 cm, an EF of 0·53, an LVET of 95 per cent, a normal left atrium of 3·3 cm, and no pathological extra sounds.

CASE 24

This was a 48-year-old woman who was well until January 1976 when she developed exertional dyspnoea and peripheral oedema. The cardiac volume was 650 ml/m². She was treated with digoxin and frusemide, and her dyspnoea increased slowly. She was referred to this centre in September 1976. Investigations showed an LVEDD of 7·1 with mechanical alternans, an EF of 0·12 and 0·35 in alternate beats, an LVET of 65 per cent, and loud extra sounds. She was admitted to our hospital on 27 September. On admission she had no dyspnoea at rest but could not walk even on the flat. Auscultation showed a tachycardia of 120 beats/min, third and fourth heart sounds, but no systolic murmur. The blood pressure was 130/90 mmHg and the heart size 760 ml/m². Investigations showed (Table 3) an LVEDD of 7·4 cm, an EF of 0·30 with tiny contractions, and an LVET of 66 per cent. She was considered to have very severe COCM. Cardiac catheterisation showed a heart rate of 122, an arterial pressure of 128/100 mmHg, a pulmonary artery pressure of 59/35 mmHg, and a right atrial pressure of 16 mmHg; the cardiac index was 1·6 l/min per m² and stroke index 13 ml/m². After 15 mg metoprolol intravenously, the corresponding pressures were 108/83, 47/30, and 14 mmHg, the cardiac index was 1·3, and the stroke index 12. She was therefore given metoprolol orally 25 mg twice daily in addition to digitalis and frusemide. A distinct improvement was noted with a reduction in her dyspnoea. The blood pressure was unchanged, the heart rate decreased to 90 to 100 beats/min, and the extra sounds became much quieter. The metoprolol dosage was increased to 50 mg twice daily, and the patient improved further so that she could walk freely without discomfort. On 20 October she developed left-sided chest pain and was noted to have a temperature for two days. She showed no clinical signs of heart failure thereafter.

Nine days later the patient was found dead. Necropsy disclosed a dilated heart of 550 g. The coronary arteries showed no stenosis and there were no signs of myocardial ischaemia. Two small pulmonary emboli were found.

Non-invasive findings

Forty-six studies were performed before, and 53 after, the start of beta-receptor blockade in 23 patients. Four patients were not reinvestigated before they died (cases 9, 11, 12, and 24) and one patient (case 5) was not investigated before the start of treatment. The observation period was divided into four parts; 1 to 6, 7 to 12, 13 to 24, and greater than 24 months after the start of beta blockade. If a patient underwent more than one investigation during the same period, the mean values were taken. The results are shown in Fig. 3 and 4.

From Fig. 3A and Table 3 it can be seen that the LVEDD decreased in 12 patients. In three patients the LVEDD increased (cases 3, 6, and 8), and in 11 patients it remained essentially unchanged. The EF (Fig. 3B) increased in 10 patients, decreased slightly in three (cases 18, 19, and 27), and was unchanged in five. The overall increase in the EF during the first six months was $0{\cdot}32 \pm 0{\cdot}02$ to $0{\cdot}42 \pm 0{\cdot}04$ ($p < 0{\cdot}05$). In the seven patients in whom the EF could be measured before and after two years of treatment, it increased from $0{\cdot}31 \pm 0{\cdot}05$ to $0{\cdot}52 \pm 0{\cdot}05$ ($p < 0{\cdot}01$). The mean V_{CF} was calculated before and after the start of treatment in 16 patients. As can be seen from Fig. 3C an increase occurred in seven patients and a decrease in two (cases 16 and 18) while in seven patients it remained unchanged. The LVET increased in seven patients, decreased in two (cases 21 and 27), and remained unchanged in the others (Fig. 3D).

The amplitude of the third heart sound, measured from the apical phonocardiogram, decreased in most patients (Fig. 4A). However, three of the patients (cases 18, 21, and 27) showed an increase. Overall, the amplitude of the third heart sound decreased from 11 ±2 to 5 ±1 mm ($p < 0{\cdot}02$) and the amplitude of the fourth heart sound showed similar changes, with a decrease in 12 patients and an unchanged or increased amplitude in four patients (Fig. 4B). The RFW/H ratio decreased significantly overall in all observation periods (Fig. 4C). During the first six months the RFW/H ratio decreased from 19 ±3 to 10 ±4 per cent

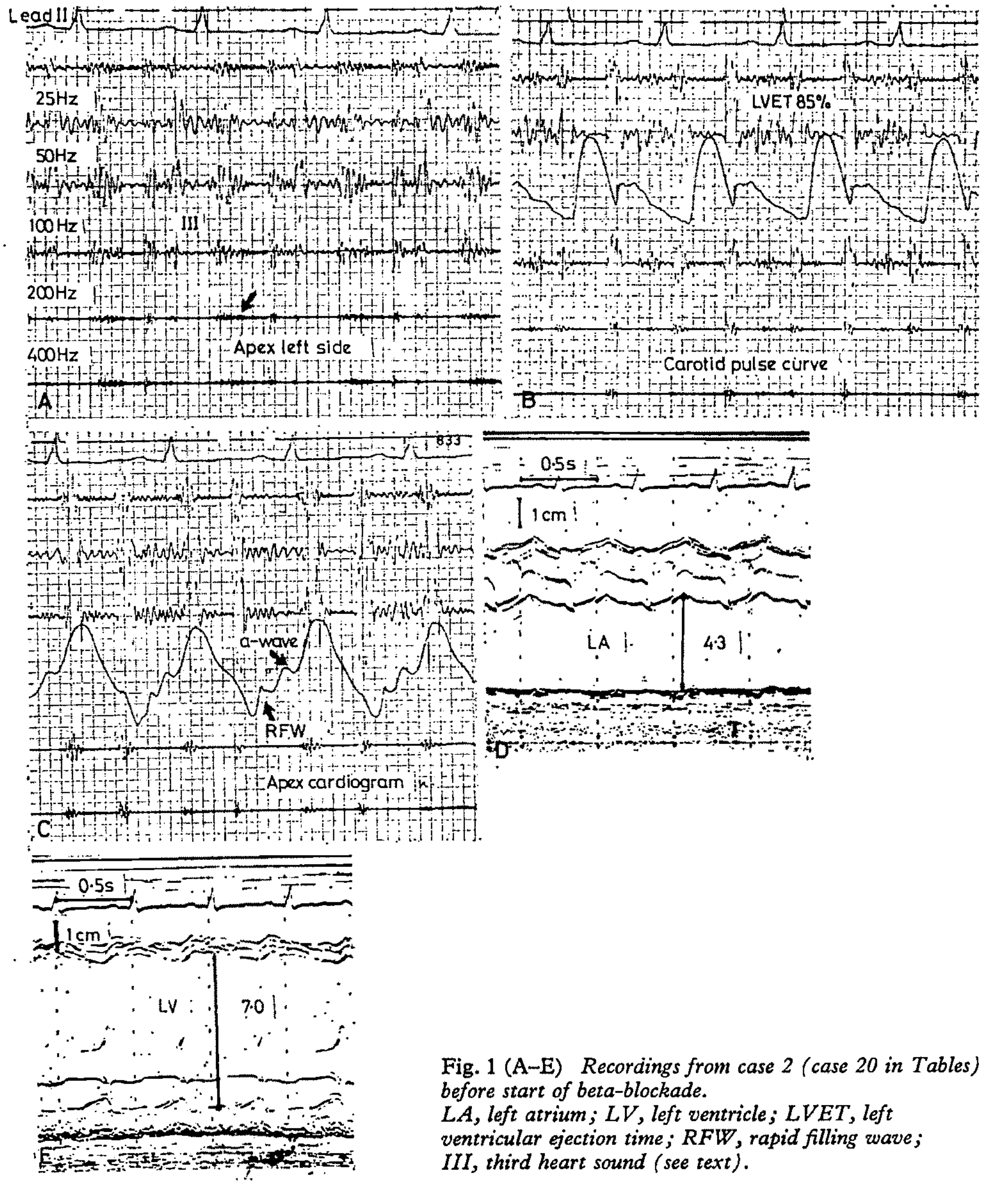

Fig. 1 (A–E) *Recordings from case 2 (case 20 in Tables) before start of beta-blockade.*
LA, left atrium; LV, left ventricle; LVET, left ventricular ejection time; RFW, rapid filling wave; III, third heart sound (see text).

($p < 0{\cdot}01$). Only one patient showed an increase during this time (case 27) and two patients had essentially unchanged RFW/H ratios (cases 15 and 21). The a/H ratio decreased significantly during the first six months ($p < 0{\cdot}05$). Two patients showed an increase in the a/H ratio (cases 19 and 27) and in five patients it was unchanged (cases 1, 4, 8, 18, and 26) (Fig. 4D).

The pronounced improvement in the EF was related to a reduction of the third heart sound amplitude or the RFW (cases 1, 7, 16, and 17). In most cases, the LVET increased at the same time. The increase in the EF was, in most cases, related to a reduction of LVEDD. In some cases this reduction was not observed, indicating a change in the degree of mitral regurgitation (case

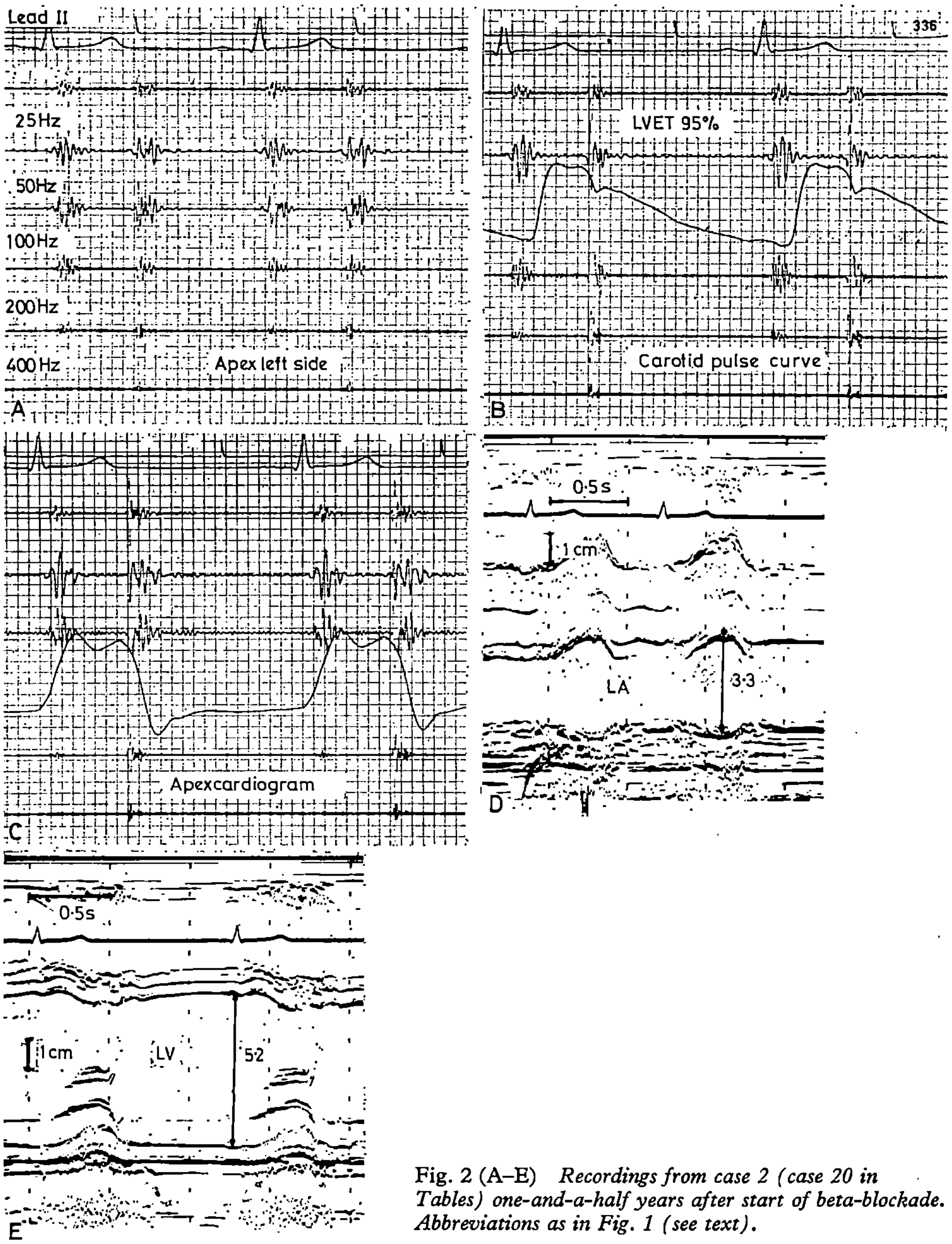

Fig. 2 (A–E) *Recordings from case 2 (case 20 in Tables) one-and-a-half years after start of beta-blockade. Abbreviations as in Fig. 1 (see text).*

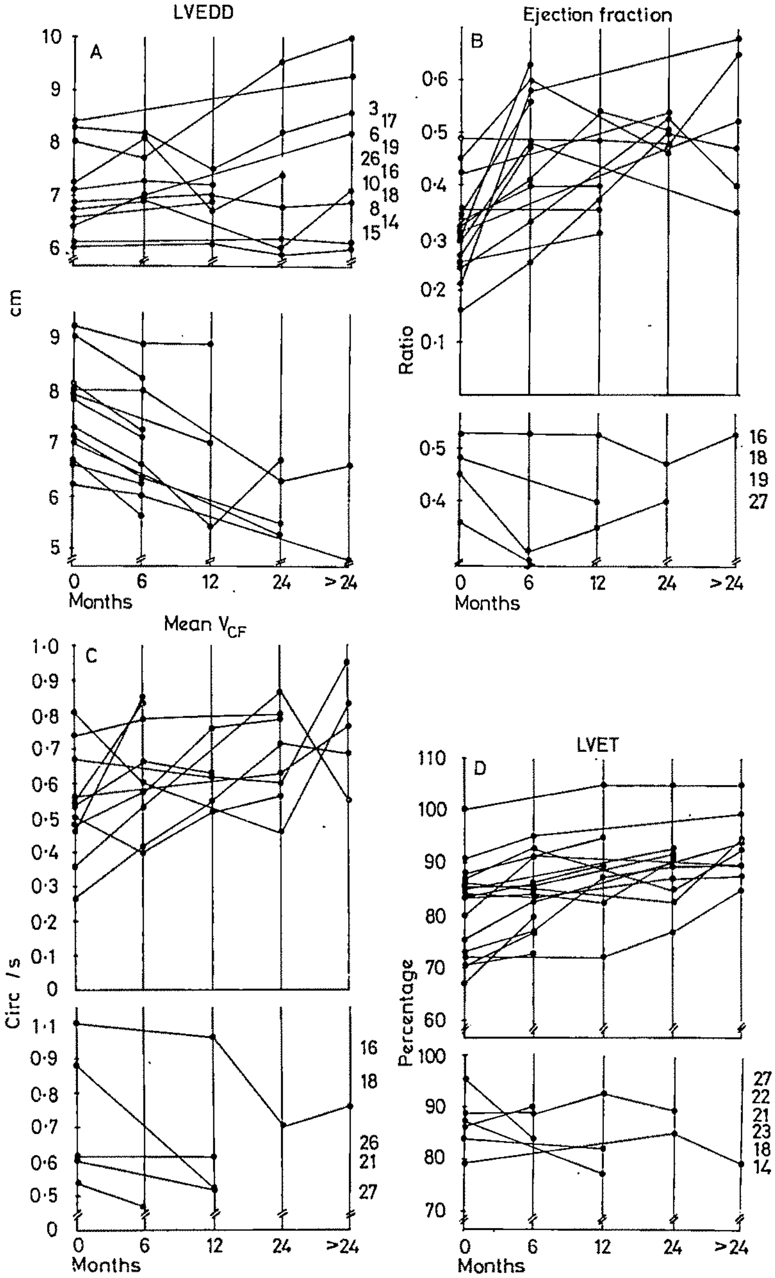

Fig. 3 (A–D) and 4 (A–D) *Haemodynamic variables before and during treatment with beta-blockers. The treatment period is divided into four parts: 0 to 6, 7 to 12, 13 to 24, and > 24 months. Each period is represented by a vertical line. Investigations performed during a period are shown by a dot on that line. If more than one investigation was carried out, the mean values are shown. Values for each individual patient are connected. The upper part of each figure shows patients who have increased values, the lower part patients who have decreased values for each variable. Patients with unchanged values lie in between. On the right are the case numbers referring to Table 1. The position of the number corresponds to the dots on the left vertical line. For exact values, see Table 3.*

17). The third heart sound amplitude and the RFW always showed corresponding changes. A reduction of these variables correlated with an improvement in the clinical condition and this occurred usually in the first two weeks. This correlation can be seen in the comparison of changes in functional groups (Table 2 and Fig. 4A–D). In three patients (cases 18, 21, and 27) the EF and LVET were either unchanged or reduced and the third heart sound and RFW increased. Cases 18 and 21 complained of gastrointestinal discomfort and showed poor motivation for treatment. They had no problems with the medication during inpatient treatment, but their compliance as outpatients was questionable. Case 27 deteriorated during the first four months on metoprolol 50 mg twice a day. On

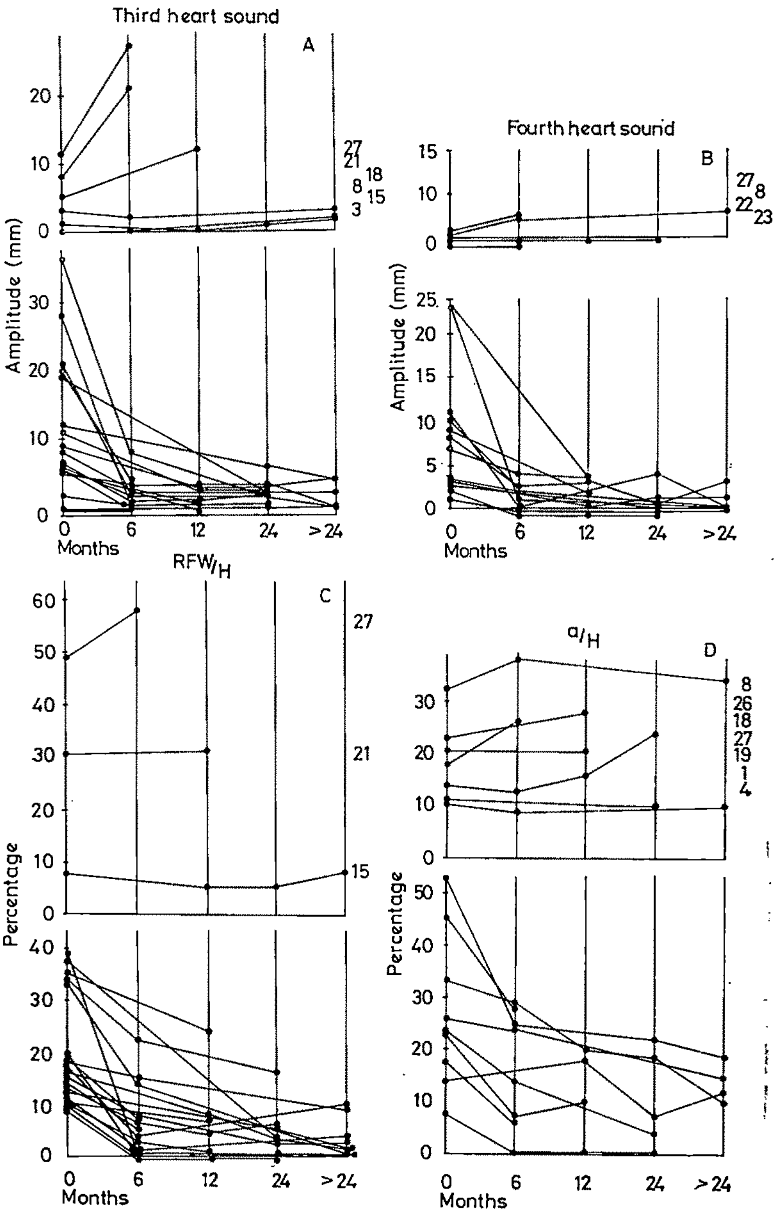

Fig. 4

investigation four months after the start of beta-blockade, the third heart sound had increased to 50 mm and the RFW/H ratio to 110 per cent (sic) while the EF was reduced from 0·29 to 0·19. The patient's clinical condition became critical and he developed severe peripheral oedema which did not respond to increased doses of frusemide. In desperation, the metoprolol dosage was increased to 100 mg twice a day. The patient improved dramatically in the following two weeks, peripheral oedema and dyspnoea at rest disappearing. Further investigation showed that the third heart sound was then reduced to 5 mm and the RFW/H ratio to 6 per cent. The mean values for the last two studies, both performed within six months of the start of beta-blockade, are shown in Table 3 and Fig. 3 and 4. The figures do not illustrate the observed changes in this patient.

The relation of heart rate to the other variables in Fig 3 and 4 was analysed. Mean values from all studies before and during treatment have been used. No correlation was found between the reduction in heart rate induced by beta-blockade and changes in EF, LVET, RFW/H, or a/H ratios. Before treatment there was a weak correlation between heart rate and third heart sound amplitude ($r = 0{\cdot}59$; $n = 22$) but this disappeared during treatment. The reduction in third heart sound amplitude correlated weakly with the heart rate change ($r = 0{\cdot}59$) (Fig. 6).

HEART VOLUME

Chest *x*-ray film was taken in all patients before and in 21 patients during beta-blocker treatment. The heart volumes are shown in Fig. 5A. The volume decreased significantly in eight patients, with a distinct increase in three patients. The remaining 10 patients showed no definite changes. In the two patients with the largest hearts, a distinct reduction was seen.

EXERCISE TESTS

Dynamic exercise tests were performed in 22 patients before the start of treatment. Four patients were bed-ridden and were not exercised at this time, but two were investigated during follow-up. The pretreatment load was arbitrarily recorded as 40 watts, which was the lowest corresponding value from the other patients. The 13 patients in the upper part of Fig. 5B increased their exercise capacity from 91 ± 12 to 117 ± 10 watts ($p < 0{\cdot}01$). The post-exercise heart rate was significantly lower at six months ($p < 0{\cdot}01$). The work pulse after exercise increased by 19 per cent, from 37 ± 3 to 43 ± 3 joules/beat ($p < 0{\cdot}02$). Systolic blood

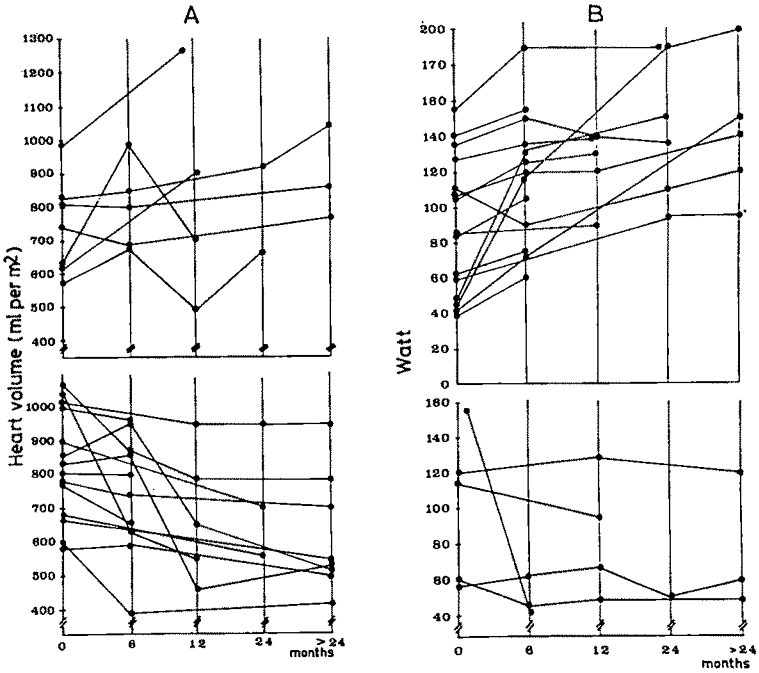

Fig. 5 (A) *Radiological heart volume in ml/m² before and during treatment with beta blockers.* (B) *Maximum workload (watts) before and during treatment with beta-blockers. The upper part of each figure shows patients who have increased values; the lower part, patients who have decreased values.*

pressure showed no significant changes during rest or exercise.

Invasive investigation

Mainly non-invasive techniques were used in this study for the diagnosis of COCM and assessment of the severity of the disease and the results of treatment. However, in four of the first patients treated, cardiac catheterisation was performed on two occasions, separated by an interval of two to 13 months (cases 1, 2, 6, and 7). These investigations formed part of the routine clinical assessment and were not related to the study design. The results, however, support the findings from the non-invasive investigations (Fig. 7). Cardiac output increased in three of these four patients and this was especially pronounced in case 1 who showed an increase from 1·9 to 5·1 l/min. The heart rate was reduced in all patients but one. The stroke volume increased conspicuously in three of the patients and pulmonary artery diastolic pressure was reduced in three. A distinct reduction in systemic vascular resistance was seen in case 1, in whom the most obvious increase in cardiac output occurred. The brachial artery and systolic blood pressure increased in all patients.

In nine patients left ventricular angiography and echocardiography were performed within a space of one week. The EF calculated from these investigations correlated well (r=0·92) (Fig. 8).

Discussion

All the patients in this study were diagnosed as having congestive cardiomyopathy, according to the criteria proposed by Goodwin and Oakley.[7] Coronary artery disease was excluded by history, and by coronary angiography in 14 patients. The diagnosis and the assessment of the severity of the disease were based upon a series of non-invasive investigations which included phonocardiograms, apex cardiograms, pulse curves from the carotid artery, jugular vein, and liver, and echocardiograms. The advantages of this non-invasive programme were that it gave information on the severity of myocardial dysfunction and that it could be repeated several times during follow-up. Measure-

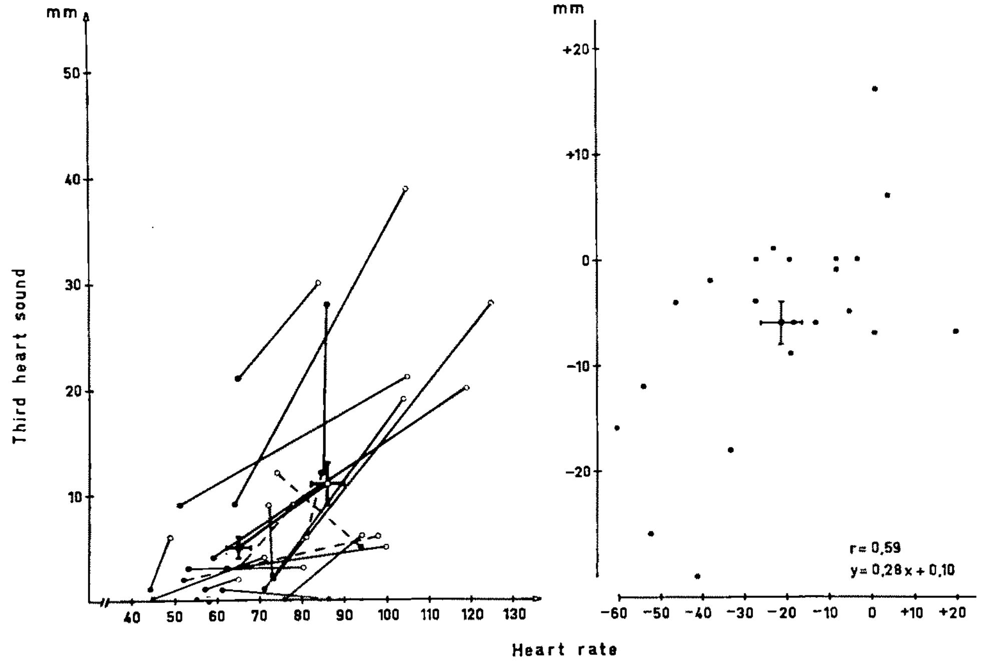

Fig. 6 *Relation between heart rate and amplitude of third heart sound, before (○) and during (●) treatment with beta-blockers. The left-hand side of the figure shows absolute changes, and the right-hand side shows changes in heart rate and third heart sound amplitude during treatment compared with control values. Values during treatment are mean values of all observations. Interrupted lines refer to patients with atrial fibrillation.*

ment of the variables LVEDD, EF, mean V_{CF}, LVET, third and fourth heart sounds, "a" wave, and RFW/H made it possible to grade myocardial dysfunction, allowing the identification of subgroups within this population of patients with generalised left ventricular myocardial disease. Of the 28 patients included in this study, 24 were considered to have severe myocardial dysfunction, and four less severe dysfunction. It is known that the prognosis is poor for patients with COCM and symptoms of heart failure despite optimal treatment with digitalis and diuretics. The mortality in the 24 patients with severe failure was 17, 34, and 48 per cent after one, two, and three years, respectively. In a comparable group of 13 patients with COCM who were treated at this centre without beta blockers, the mortality was 54, 81, and 90 per cent after one, two, and three years, respectively.[14] It is known that survival of patients with heart disease is generally related to myocardial function, and the prognosis worsens with increasingly severe heart failure.[2 15–17] It is therefore possible that an improvement in myocardial function with chronic beta-blockade could improve the prognosis. Another possible protective effect might be by prevention of ventricular fibrillation. It is known from animal experiments that, at least in ischaemic heart disease, beta-blockers reduce the incidence of ventricular fibrillation.[18] In three studies in postinfarction patients, improved survival has been reported with beta-blockers given for two years after the acute illness.[19–21] The effects of beta-blockade on myocardial function, however, were not investigated in any of those studies. Beta-blockade might prevent sudden cardiac death through mechanisms quite independent of any effect on myocardial systolic function.

In this study 28 patients were treated with beta-blockers for six to 62 months except for four patients who died within two months. All patients also received unchanged or reduced doses of digitalis and diuretics during this treatment period. It was necessary to introduce beta-blockade slowly as otherwise dyspnoea tended initially to increase. As assessed by the clinical findings, myocardial function improved in 15 patients, while in 12 it remained unchanged and in one it deteriorated. All eight patients in functional group IV (New York Heart Association criteria) had pronounced capacity-limiting dyspnoea. One patient died from progressive cardiac failure, despite withdrawal of treatment, whereas myocardial function was improved in the others as assessed by non-invasive investigations and clinical evaluation. The improvement was most obvious during the first month. Three of these patients, initially in functional group IV, went back to work. Of the patients in functional group III, seven were much improved by treatment while 11 were unchanged and one deteriorated. The observations from this study are in agreement with the results in seven patients reported earlier.[6] In the 16 patients given placebo before the start of treatment, myocardial function was either unchanged or deteriorated. The improvement of

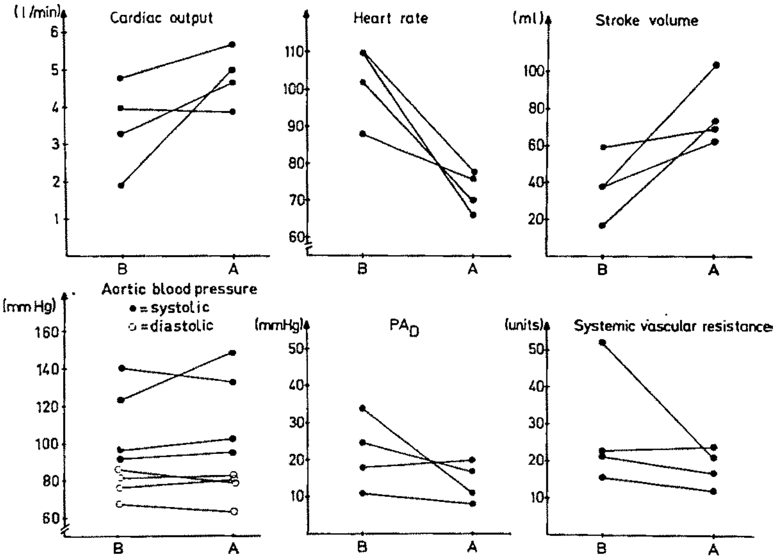

Fig. 7 *Haemodynamic findings before and two to 13 months after the start of beta-blockade in four patients with congestive cardiomyopathy (case no. 1, 3, 6, and 7).*
PA_D, pulmonary artery diastolic pressure; B, before and A, after start of beta-blockade.

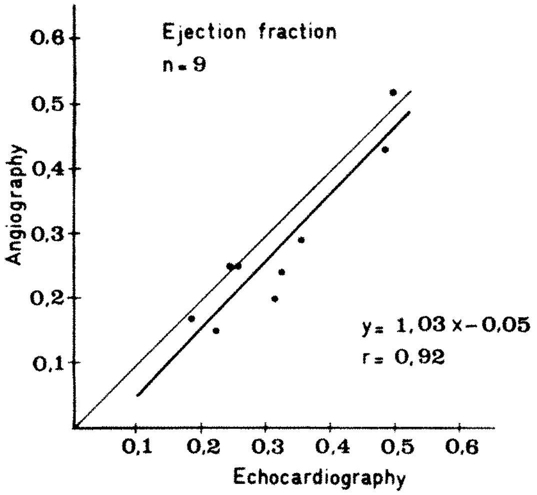

Fig. 8 *Ejection fraction calculated from left ventricular angiograms and echocardiograms. In each patient the investigations were performed within one week.*

myocardial function which occurred after the start of beta-blockade was very clear and cannot be considered to be a spontaneous change independent of treatment. The response to beta-blockade was very variable and it was not possible to predict the effects of treatment from initial clinical findings or investigations. The results of the pilot study[6] suggested that patients with a higher heart rate responded better to beta-blockade. This was not confirmed in this study. The reduction of heart rate did not correlate to the change in EF, LVET, RFW/H, or a/H ratios. However, patients with severe heart failure usually do have a tachycardia. If it is myocardial disease *per se* that is influenced by beta-blockade, the selection of patients by heart rate could be misleading. Patients with an LVEDD >7 cm have a lower one-year mortality if treated with the addition of beta-blockade than those with conventional treatment.[14] It seems that in most patients the beneficial effects of beta-blockade occur within one to three months of the start of treatment, and that the improvement is stable thereafter. Some patients, however, continue to improve for a longer time (cases 1, 17, and 20). The improvement of myocardial function produced by beta-blockade was shown in this study as an improvement of functional class and exercise capacity, and by the improved results of non-invasive investigations. Systolic as well as diastolic myocardial function improved, and the changes included a reduction of LVEDD, an increased EF and LVET, a reduced amplitude of third and fourth heart sounds, and a reduction in the rapid filling wave and "a" wave. An increase in LVET, EF, and mean V_{CF} represents an improvement in myocardial systolic function. As mentioned earlier, the degree of secondary mitral regurgitation is important for the evaluation of EF and mean V_{CF}. An increase in these variables can occur with increased mitral regurgitation but indicates improved myocardial systolic function in combination with an increase in LVET and/or the disappearance of an apical systolic murmur. Changes in heart sounds, the rapid filling wave, and the "a" wave corresponded to changes in left ventricular distensibility induced by beta-blockade. Changes in the third heart sound and RFW were frequently related and were useful early indicators of the therapeutic effect. It has been reported that beta blockade in patients with ischaemic heart disease causes an increase in left ventricular distensibility as well as increased left ventricular end-diastolic volume.[22] In this study, however, there was no increase in LVEDD. In contrast, it often decreased, with signs of improved diastolic function.

The improvement in cardiac function and in the patients' general condition with beta-blockade could not be explained on the basis of spontaneous improvement in selected subjects. All patients referred to this centre suspected of having COCM have been investigated and all those in whom the diagnosis was confirmed were included in the study. Only patients with evidence of grossly impaired myocardial function (generally in functional group III or IV, according to the New York Heart Association criteria) were given chronic beta-blocker treatment. In a separate study,[13] the effect of withdrawal of beta-blockade has been investigated in 13 of the patients reported here. It was found that withdrawal of treatment caused a deterioration of myocardial function and in several of the patients led to a distinct exacerbation of their symptoms. This strongly supports the view that the improvement seen in the patients in this study is related to the beta-blocker treatment.

Phaeochromocytoma may induce cardiomyopathy with heart failure,[23 24] clearly showing a connection between high concentrations of catecholamines and this condition. In the treatment of these patients, beta-blocking agents are used to protect the myocardium from the influence of catecholamines until the tumour is removed sugically.[25] Furthermore, prolonged bed rest has been found to cause an improvement in patients with COCM after three to 12 months,[5] possibly because bed rest causes a reduction of cardiac work and a lower level of sympathetic activity. If this is the case, similar mechanisms may be involved in the beneficial effects of long-term bed rest and chronic beta-blockade. Animal experiments have shown

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that the spontaneous hereditary congestive cardiomyopathy of Syrian hamsters can be counteracted by beta-blockade.[26 27] Long-term treatment of rats with catecholamines has been found to cause diffuse myocardial degeneration as well as hypertrophy.[28] Thus, it may be concluded that other clinical observations, besides our own, together with animal data, support the hypothesis that catecholamines are involved in the development of some forms of cardiomyopathy and that reduced sympathetic activity by beta-receptor blockade can prevent the progress of the condition. This view is supported by our present findings of a beneficial effect of chronic beta blockade on COCM. The suggested role of catecholamines and sympathetic activity in the development of the condition remains to be proved, and studies are in progress to find out whether there is primary sympathetic overactivity in patients with COCM or an increased sensitivity to sympathetic stimulation.

This study clearly demonstrates that chronic beta-receptor blockade may cause a significant improvement in myocardial function and relief of symptoms in patients with COCM. The improvement occurs in patients with moderate as well as severe heart failure. The patients responding best to beta-blockade could not be predicted by the methods used and it is therefore suggested that beta-receptor blockade should be added to conventional treatment with digitalis and diuretics in all patients with COCM. More experience of this treatment regimen, however, is needed in order to allow identification of the patients most suitable for it.

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References

[1] Hamby RI. Primary myocardial disease. A prospective clinical and hemodynamic evaluation in 100 patients. *Medicine* 1970; **49:** 55–78.

[2] Kreulen TH, Gorlin R, Herman MV. Ventriculographic patterns and hemodynamics in primary myocardial disease. *Circulation* 1973; **47:** 299–308.

[3] Hess OM, Turina J, Goebel NH, Krayenbühl HP. Klinischer Verlauf der kongestiven Kardiomyopathie. *Schweiz Med Wochenschr* 1976; **106:** 1577–9.

[4] Kübler W, Zebe H, Mäurer W, Mehmel H, Zekl G. Die kongestive Kardiomyopathie. *Munch Med Wochenschr* 1976; **118:** 751–8.

[5] McDonald CD, Burch GE, Walsh JJ. Prolonged bed rest in the treatment of idiopathic cardiomyopathy. *Am J Med* 1972; **52:** 41–50.

[6] Waagstein F, Hjalmarson Å, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br Heart J* 1975; **37:** 1022–36.

[7] Goodwin JF, Oakley CM. The cardiomyopathies. *Br Heart J* 1972; **34:** 545–52.

[8] Wikstrand J, Nilsson K, Wallentin J. Distortion of non-invasive cardiac pulse curves. A capillary-damped pick-up and a calibration unit for apexcardiograms and other pulse curves. *Br Heart J* 1977; **39:** 995–1005.

[9] Meiners S. Messmethoden zur Analyse der Herz- und Kreislaufdynamik. *Freiburger Colloquium, München,* 1958: 84–98.

[10] Willems J, Kesteloot H. The left ventricular ejection time. Its relation to heart rate, mechanical systole and some anthropometric data. *Acta Cardiol (Brux)* 1967; **22:** 401–25.

[11] Pombo JF, Troy BL, Russell RO Jr. Ventricular volumes and ejection fraction by echocardiography. *Circulation* 1971; **43:** 480–90.

[12] Cooper RH, O'Rourke RA, Karliner JS, Peterson KL, Leopold GR. Comparison of ultrasound and cineangiographic measurements of the mean rate of circumferential fiber shortening in man. *Circulation* 1972; **46:** 914–23.

[13] Swedberg K, Hjalmarson Å, Waagstein F, Wallentin I. Adverse effects of beta blockade withdrawal in patients with congestive cardiomyopathy. *Br Heart J* 1980; **44:** 134–42.

[14] Swedberg K, Hjalmarson Å, Waagstein F, Wallentin I. Prolongation of survival in congestive cardiomyopathy by beta-receptor blockade. Preliminary communication. *Lancet* 1979; **1:** 1374–6.

[15] Feild BJ, Baxley WA, Russell RO Jr, *et al.* Left ventricular function and hypertrophy in cardiomyopathy with depressed ejection fraction. *Circulation* 1973; **47:** 1022–31.

[16] Vedin A, Wilhelmsen L, Wedel H. Prediction of death and reinfarction after initial myocardial infarction. *Acta Med Scand* 1977; **201:** 309–16.

[17] Loogan F, Kuhn H. Classification and natural history of primary cardiomyopathies. In: Riecker G, Weber A, Goodwin J, eds. *Myocardial failure.* Berlin: Springer, 1977: 232–50.

[18] Corr PB, Witkowski FX, Sobel BE. Mechanisms contributing to malignant dysrhythmias induced by ischemia in the cat. *J Clin Invest* 1978; **61:** 109–19.

[19] Ahlmark G, Saetre H, Korsgren M. Reduction of sudden deaths after myocardial infarction. *Lancet* 1974; **2:** 1563.

[20] Wilhelmsson C, Vedin JA, Wilhelmsen L, Tibblin G, Werkö L. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. *Lancet* 1974; **2:** 1157–64.

[21] Multicentre International Study. Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. *Br Med J* 1975; **3:** 735–40.

[22] Coltart DJ, Alderman EL, Robison SC, Harrison DC. Effect of propranolol on left ventricular function, segmental wall motion, and diastolic pressure-volume relation in man. *Br Heart J* 1975; **37:** 357–64.

[23]Kline IK. Myocardial alterations associated with pheochromocytomas. *Am J Pathol* 1961; **38:** 539–47.

[24]Engelman K, Sjoerdsma A. Chronic medical therapy for phaeochromocytoma. *Ann Intern Med* 1964; **61:** 230–41.

[25]Baker G, Zeller NH, Weitzner S, Leach JK. Pheochromocytoma without hypertension presenting as cardiomyopathy. *Am Heart J* 1972; **83:** 688–93.

[26]Jasmin G, Bajusz E. Polymyopathie et cardiomyopathie héréditaire chez le hamster de Syrie. Inhibition sélective des lésions du myocarde. *Ann Anat Pathol (Paris)* 1973; **18:** 49–66.

[27]Lossnitzer K, Janke J, Hein B, Stauch M, Fleckenstein A. Disturbed myocardial calcium metabolism: a possible pathogenetic factor in the hereditary cardiomyopathy of the Syrian hamster. *Recent Adv Stud Cardiac Struct Metab* 1975; **6:** 207–17.

[28]Källfelt BJ, Waldenström AP, Hjalmarson ÅC. Effects of adrenaline *in vivo* on protein synthesis, mechanical performance and sensitivity to ischemia in the perfused rat heart. *J Mol Cell Cardiol* 1977; **9:** 383–98.

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Br Heart J 1980; **44:** 134–42

Adverse effects of beta-blockade withdrawal in patients with congestive cardiomyopathy

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SUMMARY Fifteen patients with congestive cardiomyopathy who had improved conspicuously on chronic administration of a beta-blocker were studied after withdrawal of the drug. In six patients there was a pronounced deterioration of their clinical condition, and in all of the remaining patients there was a significant decrease in ejection fraction, and signs of compromised diastolic function with pathological apex curves and an increase in third heart sound. All these changes were reversed within a few weeks to a few months after readministration of beta-blocking drugs. This study supports the idea that an aetiological factor in congestive cardiomyopathy may be a pathological response to sympathetic stimulation which could be partly controlled by administration of beta-blocking drugs.

An improvement in myocardial function and general condition with chronic beta-blockade in patients with congestive cardiomyopathy (COCM) was first reported in 1975,[1] and this has been confirmed in a more extensive recent study.[2 3] It has been known for many years that in patients with heart failure there is a compensatory increase in sympathetic nervous activity to counteract the depressed myocardial function.[4] Furthermore, beta-blockade is thought to aggravate heart failure and this treatment is said to be contraindicated in such patients. Taking this into account, the finding that beta-blocking agents could cause an improvement in myocardial function in patients with congestive cardiomyopathy and heart failure was surprising and unexpected.

In this study beta-blockade was withdrawn in patients with COCM after long-term administration. This was done for two reasons. First, the effects of withdrawal should give useful information about the role of beta-blockade in the improvement in myocardial function after long-term treatment. Second, valuable information could be obtained about the mechanisms underlying the observed beneficial effect of beta-blockade in these patients. Would there be an immediate deterioration in the patients' condition in parallel with the fall in tissue concentration of the beta-blocking agent? Would the improved myocardial function persist even without beta-blockade, indicating that the treatment had been curative and not merely functioning by modulating heart rate and pressure development?

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Patients and methods

In January 1978, 19 patients with congestive cardiomyopathy who had undergone chronic beta-blockade for at least six months were considered for the withdrawal study. Two patients who had been on beta-blockers for four-and-a-quarter and five years refused to discontinue the treatment. One patient was living far from Göteborg and could not take part in a closely controlled study. One patient had recently required an increase in metoprolol dosage to counteract a deterioration in cardiac function and it was therefore judged unethical to discontinue treatment. The remaining 15 patients were informed about the study and agreed to take part.

The duration of treatment and the daily dose of a beta-blocking agent before withdrawal are shown in the Table. All patients had taken the same dose of metoprolol for at least one month before investigation. Treatment with digitalis and diuretics continued unchanged. The patients were assessed (see below) at least once weekly during the first month after withdrawal of beta-blockade. If changes in their general condition or signs of progressive heart failure appeared, they were reassessed immediately. In patients with no subjective or objective changes after beta-blockade, withdrawal reassessment was performed after four months. The investigations performed at each assessment included phonocardiograms from five standard areas, an apex cardiogram, pulse tracings from the carotid artery, jugular vein, and liver, and an echocardiogram, as described elsewhere.[3]

One patient (case 1) discontinued treatment, without our knowledge, in January 1978 after four years as he had been without symptoms of heart failure for three years. He was included in the study and reassessed in April 1978 at which time he showed deterioration in cardiac function, with symptoms of heart failure. He was again given metoprolol and was reassessed 29 days after restart of treatment. All investigated variables and his general condition were compared with the previous findings of June 1976. These findings are included with the prewithdrawal data of the other patients. Two patients stopped their treatment after the toxic effects of practolol were reported in 1975. The clinical findings in these patients are also reported.

Results

The duration of treatment before withdrawal, and the length of the observation period after withdrawal of beta-blockade are given for all patients in the Table. This also contains the assessment of the patients after withdrawal of the drug. The patients were observed after withdrawal for seven to 119 days (mean 72 days) before treatment was restarted. Six patients showed a clear deterioration in their clinical condition, with signs of increased heart failure. Two of these patients (cases 6 and 28) deteriorated very rapidly with a return of dyspnoea, hypotension, poor peripheral circulation, and loud third and fourth heart sounds within 14 days. Case 1 had received treatment for 48 months and returned to his poor pre-beta-blockade condition within two months of withdrawal. Case 16 complained after three weeks and was reinvestigated after 27 days. No significant abnormalities were found, and he continued without beta-blockade. He died suddenly two weeks later.

Case reports

CASE 1

This male patient was previously healthy except for recurrent duodenal ulceration treated by gastric resection at the age of 40. At the age of 53 congestive cardiomyopathy was diagnosed when moderate biventricular failure developed in connection with an upper respiratory tract infection. Over the next 18 months, he showed a progressive deterioration in cardiac function, and at the end of this period was considered to be in functional group IV (NYHA classification). Haemodynamic investigations showed a cardiac index of 1·05 l/min per m^2 and a left ventricular end-diastolic pressure (LVEDP) of 22 mmHg; the left ventricular end-diastolic diameter (LVEDD) was 6·2 cm and the ejection fraction (EF) 0·22 measured echocardiographically (Fig. 1a–e). Practolol was given initially in a very low dosage. Eventually practolol, 100 mg twice daily, was well tolerated and the patient's condition dramatically improved over two months. Reinvestigation showed an increase in the cardiac index to 2·9 l/min per m^2, normalisation of the

Table *Cardiovascular effects of withdrawal of chronic beta-blockade in patients with congestive cardiomyopathy*

Case no.	*Sex*	*Age (y)*	*Symptom duration before beta-blocker therapy (mth)*	*Duration of beta-blocker treatment (mth)*	*Present/last beta-blocker drug/dose*	*Duration of withdrawal of beta blockade (d)*	*Clinical condition*	*Non-invasive investigations*				
								EF	*3rd heart sound*	*4th heart sound*	*RFW/H ratio*	*a/H ratio*
1	M	55	15	50	A 100 mg × 2	29	Deteriorated	↓	↑	↑	↑	↓
6	M	50	23	47	M 50 mg × 3	7	Deteriorated	↓	0	↓	↑	↓
10	M	46	10	37	M 25 mg × 2	57	Unchanged	↓	↑	AF	0	AF
13	M	56	21	37	M 50 mg × 2	112	Unchanged	↑	0	0	—	—
14	M	59	24	32	M 50 mg × 3	119	Unchanged	↓	0	AF	0	AF
15	F	60	11	32	PR 40 mg × 3	103	Unchanged	↓	0	0	0	0
16	M	58	160	31	M 25 mg × 2	27	Deteriorated	↓	0	AF	↑	AF
17	M	16	4	32	M 50 mg × 3	82	Unchanged	↓	↑	↑	↑	↑
18	M	34	15	10	A 100 mg × 2	7	Deteriorated	—	—	—	—	—
19	M	49	8	22	P 40 mg × 2	92	Unchanged	↑	0	↑	0	↓
20	F	16	3	22	M 50 mg × 2	21	Unchanged	—	—	—	—	—
22	M	50	14	17	M 50 mg × 2	104	Unchanged	↓	↑	↑	↑	↑
25	M	56	18	7	M 50 mg × 2	112	Unchanged	↓	0	0	↑	0
26	M	18	6	7	M 25 mg × 2	59	Deteriorated	↓	↑	↑	↑	0
28	M	50	6	6	M 25 mg × 2	14	Deteriorated	↓	↑	↓	↑	↓

A, alprenolol; M, metoprolol; P, practolol; PR, propranolol; EF, ejection fraction; RFW/H ratio, rapid filling wave ratio; a/H ratio, "a" wave ratio; 0, unchanged; ↑, increased; ↓, decreased; —, not investigated; AF, atrial fibrillation.

resting LVEDP, and a reduction of the exercise LVEDP; the EF had increased to 0·58 and the LVEDD had decreased to 4·8 cm (Fig. 2). During the next two years the patient continued to improve, after which he defaulted from follow-up. Eighteen months later he was readmitted in severe biventricular failure, which had developed two months after accidental withdrawal of alprenolol. Again, the echocardiographic findings were grossly abnormal (Fig. 3) with an LVEDD of 6·7 cm, an EF of 0·23, and signs of mitral regurgitation. The findings were similar to those noted before beta-blockade was instituted. Metoprolol was given in low dosage and was well tolerated. Clinical improvement was obvious within two months of the start of treatment and continued for the next year. Reinvestigation confirmed the clinical improvement (Fig. 4), with a reduction in LVEDD to 4·7 cm and an increase in EF to 0·59.

CASE 2 (CASE 16 IN TABLE)

This male patient had previously been healthy except for diphtheria at the age of 7. At the age of 42, he developed moderate exertional dyspnoea and was considered to be in functional group II. Moderate cardiomegaly was noted on *x*-ray film. At the age of 58 he suddenly developed severe cardiac failure with pronounced cardiomegaly

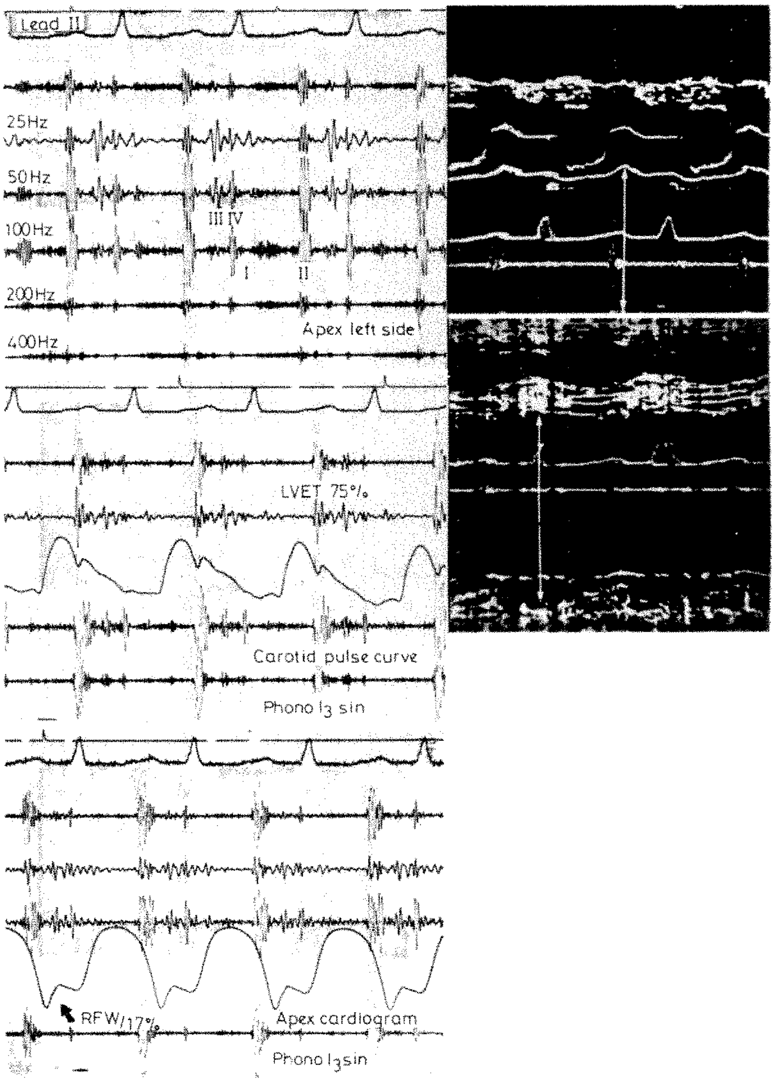

Fig. 1a–e *Non-invasive findings in case 1 during treatment with digitalis and diuretics*

(800 ml/m^2 bsa, measured radiographically). The echocardiograph showed a dilated left ventricle with an LVEDD of 7·0 cm and a moderately reduced EF of 0·50. A loud third heart sound and an apical systolic murmur were also present.

As he was in functional group III, he was given placebo according to the study procedure. Over the next three months, however, his functional status deteriorated to group IV, and beta-blockade was therefore instituted. Over the following year his clinical condition steadily improved with a distinct increase in exercise tolerance, a slight increase in EF to 0·60, and virtual disappearance of the third heart sound. There was, however, no change in heart size or LVEDD. He returned to full-time work and at this time was considered to be in functional group II. After 30 months on active treatment this was withdrawn according to the study procedure. After two weeks the patient began to experience exertional dyspnoea on moderate exercise, and a moderate reduction of the ejection fraction to 0·50 and a decreased left ventricular ejection time (LVET) were shown by echocardiograph and carotid pulse respectively. As the changes were only moderate, the withdrawal phase of the study was continued. Three weeks later, however, the patient died suddenly without an increase of cardiac symptoms. Cardiac arrhythmias

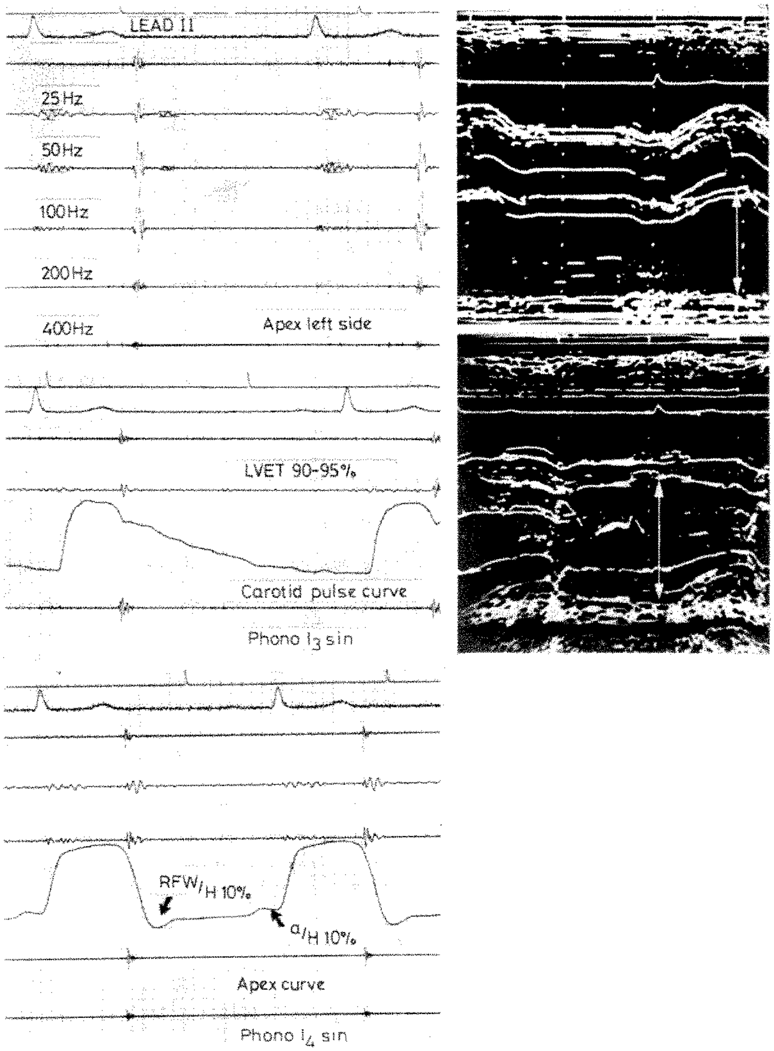

Fig. 2a–e *Non-invasive findings in case 1 during treatment with chronic beta-blockade*

were considered to be the immediate cause of death. At necropsy the patient was found to have a grossly dilated heart with pulmonary congestion.

CASE 3 (CASE 28 IN TABLE)

This male patient, previously healthy except for pulmonary tuberculosis controlled by chemotherapy, had suddenly developed biventricular cardiac failure six months before the start of beta-blockade. His condition deteriorated progressively despite treatment with digoxin and frusemide, and his functional grade was IV when he was considered for inclusion in the study.

Haemodynamic investigations at this time showed a cardiac index of 1·2 l/min per m^2, and a grossly dilated left ventricle with an LVEDD of 8·0 cm and an EF of 0·18 were shown echocardiographically. A loud third heart sound was present and was recorded on the phonocardiogram. Metoprolol was given initially in very low dosage. This was eventually increased to 25 mg twice daily which was well tolerated and the patient's condition improved with an increase in exercise capacity. The third heart sound decreased considerably. The EF increased to 0·42, but the LVEDD decreased only slightly to 7·2 cm. According to the study procedure, active treatment was withdrawn after six months and the patient carefully supervised in

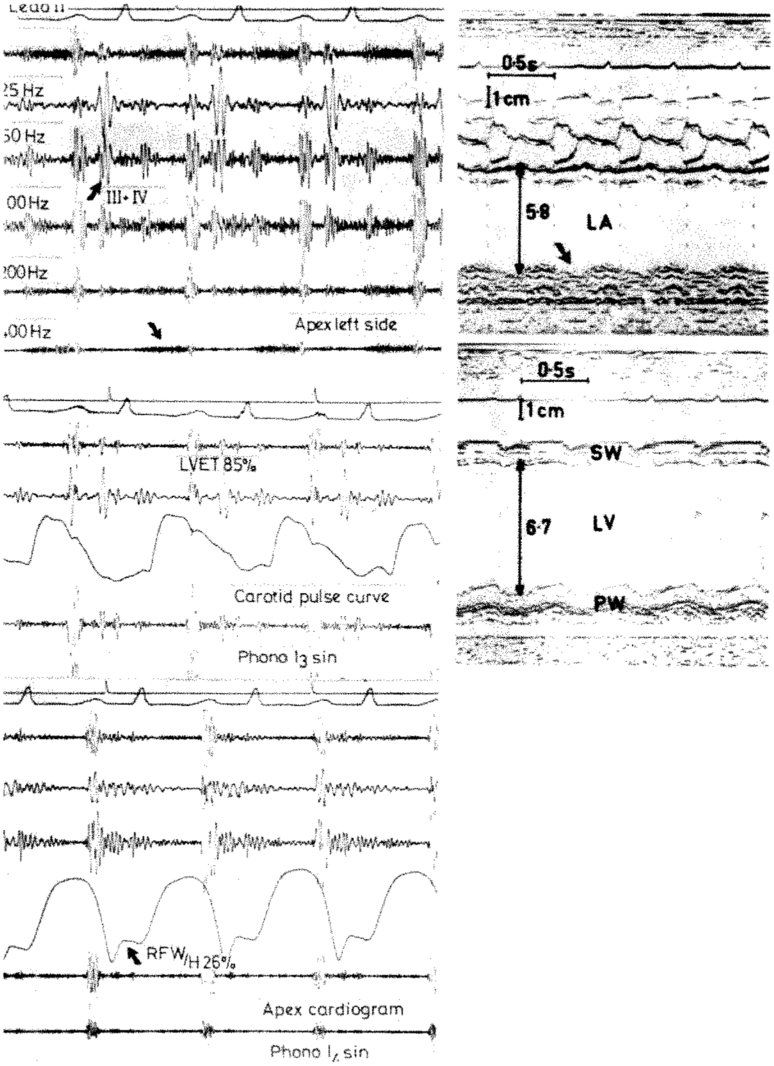

Fig. 3a–e *Non-invasive findings in case 1 after two months of withdrawal of beta-blockade.*

hospital for a period of five days. During this time there was no change in the patient's clinical condition though the third heart sound reappeared. Nine days after discharge he was readmitted semiconscious in cardiogenic shock with mechanical alternans and a systolic blood pressure of 50 to 60 mmHg. Echocardiography confirmed the clinical impression of much depressed myocardial systolic function, the EF being 0·22 and the LVEDD 7·5 cm. A very loud third heart sound was again present. Attempts to reintroduce beta-blockade were unsuccessful, but the patient responded to intravenous therapy with prenalterol, a new selective beta$_1$-agonist[5 6] given over 48 hours. After this, metoprolol was successfully reintroduced, and the patient's clinical condition and findings on investigation improved to their previous levels within two months.

Investigations

All patient data are summarised in Fig. 5–7. One patient was studied for only 21 days and no reinvestigation was performed as she had to go

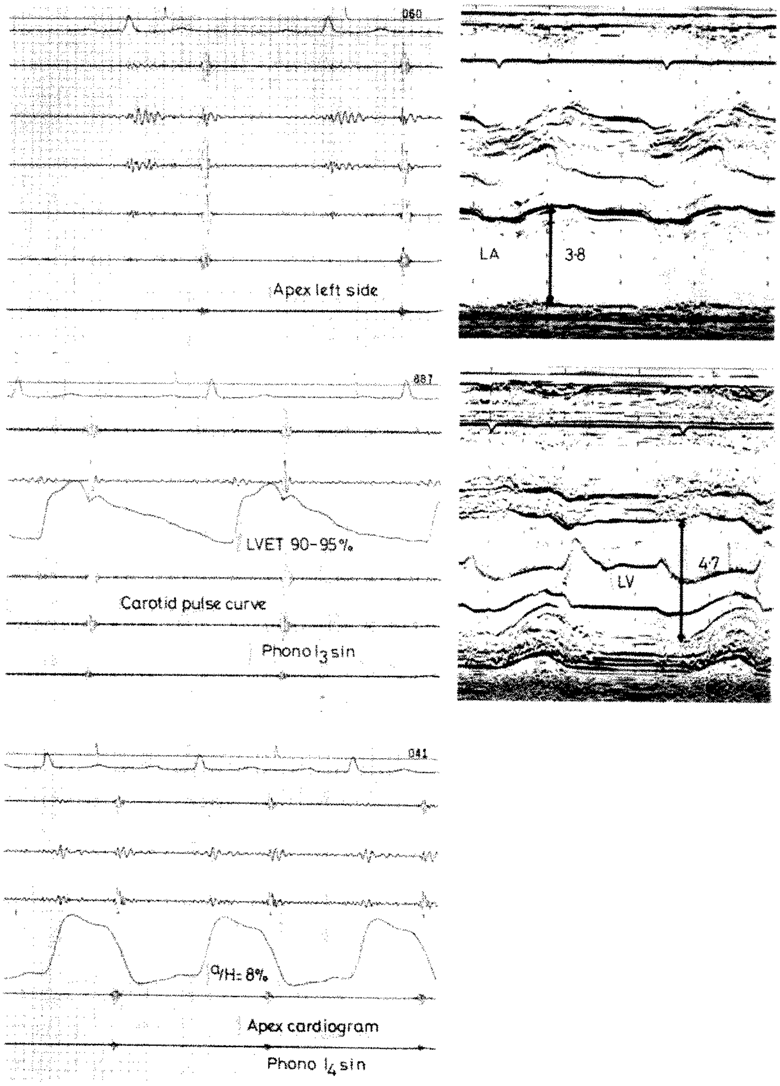

Fig. 4a–e *Non-invasive findings in case 1 one year after beta-blockade was restarted. Phono I_3sin = phonocardiogram from left third intercostal space.*

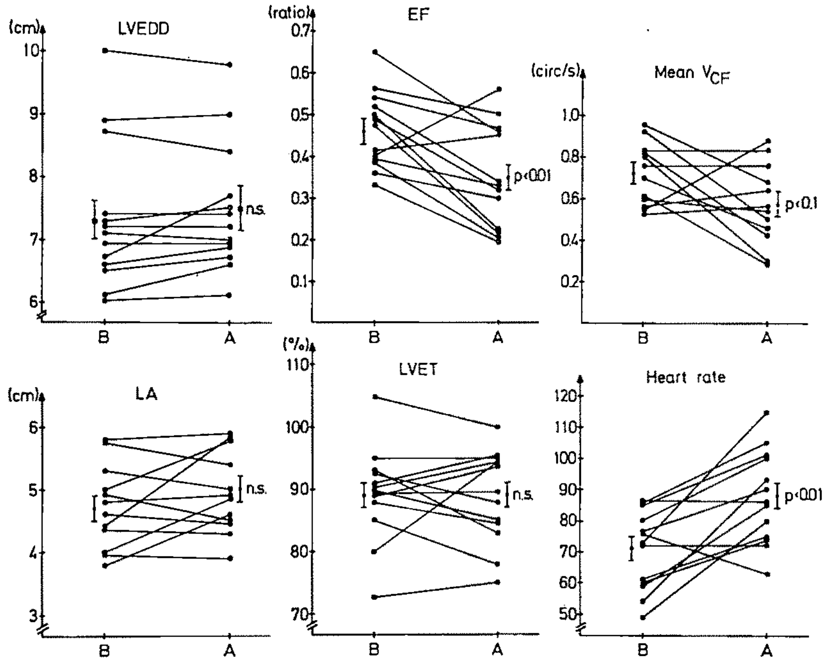

Fig. 5 *Non-invasive findings in patients with congestive cardiomyopathy on chronic beta-blockade (B) and after withdrawal of treatment (A). EF, ejection fraction; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVET, left ventricular ejection time; Mean V_{CF}, mean velcocity of circumferential fibre shortening.*

abroad (case 20). Another patient (case 18) started alprenolol treatment after seven days of withdrawal without our notice because of increasing dyspnoea and it was not possible to obtain an assessment. The other 13 patients are included in the figures. From Fig. 5 it can be seen that there was a significant fall in the EF from 0·46 ±0·03 to 0·35 ±0·03 ($p < 0{\cdot}01$), all but two patients having a lower EF after withdrawal of beta-blockade compared with before its withdrawal. No changes were seen in LVEDD. The mean velocity of circumferential fibre shortening (mean V_{CF}) was significantly reduced in six of the patients but was unchanged in five and increased in one of the patients studied. The size of the left atrium was increased in four of the patients, slightly increased in two, and unchanged in the others. The LVET was decreased in half of the patients studied and increased or unchanged in the others. All patients but one showed an increase in heart rate after beta-blockade withdrawal and the overall change in heart rate was significant for the group ($p < 0{\cdot}01$) (mean heart

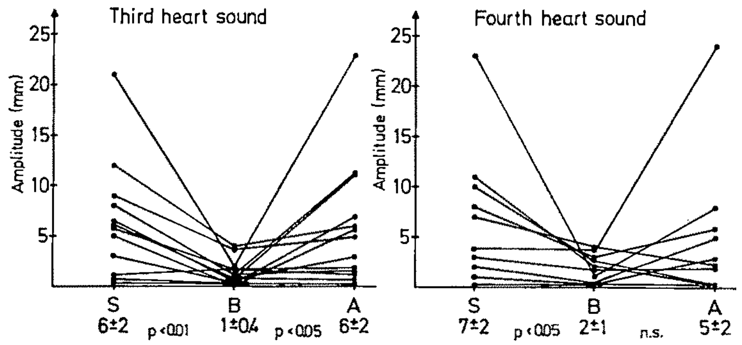

Fig. 6 *Amplitude of third and fourth heart sounds in patients with congestive cardiomyopathy before (S) and during (B) beta-blocker treatment, and after (A) withdrawal of the drug.*

rate 71 ±3 on beta-blockade; 88 ±4 beats per minute after withdrawal).

The recorded amplitude of the third heart sound increased from 1 ±0·4 to 6 ±2 mm ($p < 0·05$) and was much increased in seven of the patients (Fig. 6). Seven of the patients had no measurable third heart sound on beta-blockade and it returned in five of these patients after discontinuation of treatment. Though several of the patients also showed an increase in the fourth heart sound amplitude, the changes in this index were more variable.

The changes in RFW/H ratio are shown in Fig. 7. A significant increase in RFW occurred ($p < 0·05$) and all but two of the patients studied showed an individual increase. Changes in a/H ratio increased in some patients and decreased in others so that the mean value for the group was not changed with withdrawal of beta-blockade. Three of the patients showing a reduction in the "a" wave (cases 1, 6, and 28) had a clear increase in RFW.

During long-term treatment with beta-blockade two patients who had been on beta-blockade for 24 months and 12 months discontinued treatment without informing us. This was done by one (case 5) when the toxic effects of practolol were reported, and by the other (case 6) because of persisting exertional dyspnoea. After discontinuation of beta-blockade both developed severe cardiac failure and were brought to hospital with pulmonary oedema. When beta-blockade was reinstituted there were no further attacks of pulmonary oedema in either of them.

Discussion

The present study shows that myocardial function in congestive cardiomyopathy can be impaired by withdrawal of beta-blockers. Six of the 15 patients in the study showed a distinct deterioration in their clinical condition, with the appearance of increased dyspnoea, and three of the patients showed other signs of severe cardiac failure, such as hypotension, poor peripheral circulation, and cardiogenic shock. One of the patients who developed increased dyspnoea died suddenly 41 days after beta-blockade was discontinued. Cardiogenic shock developed two weeks after withdrawal in another patient. The ejection fraction, as measured from the echocardiogram, was decreased in 11 of the 13 patients in whom it was measured. Eight patients showed an increase in rapid filling wave and six patients a clear increase in the amplitude of the third heart sound. It appeared that the patients who had had the most dramatic improvement with beta-blockade showed the most severe deterioration after its withdrawal. The development of pulmonary oedema in the two patients who stopped treatment without our knowledge is in accord with the other observations following planned beta-blockade withdrawal. The results from this study strongly support the findings of

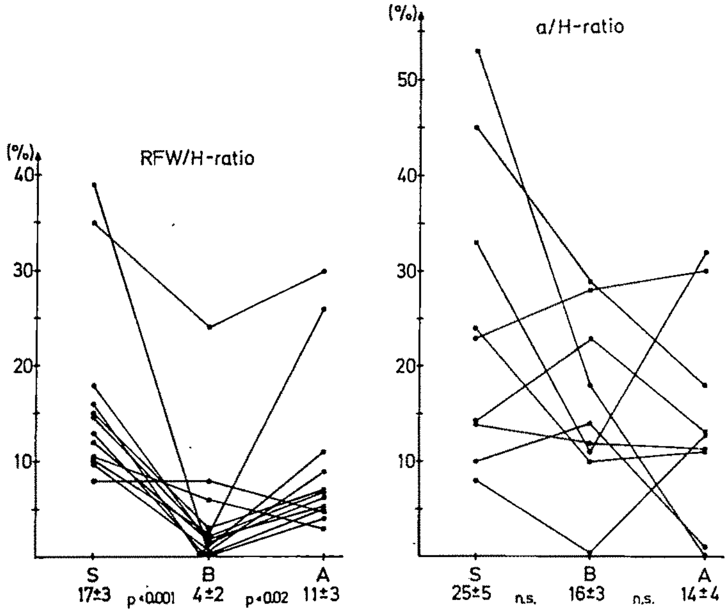

Fig. 7 *Rapid filling wave ratio (RFW/H ratio) and "a" wave ratio (a/H ratio) in patients with congestive cardiomyopathy before (S) and during (B) beta-blocker treatment and after (A) withdrawal of the drug.*

improved clinical condition and myocardial function with chronic beta-blockade, as reported before.[1-3]

A deterioration in myocardial function after discontinuation of chronic beta-blockade indicates that the treatment has not been curative. In the patients whose clinical condition deteriorated with the appearance of severe dyspnoea this appeared in two of them very soon after discontinuation of beta-blockade while there was a slower deterioration in the others. This suggests that impaired cardiac function does not correlate directly with the fall in tissue drug concentration in all patients. Beta-blockade, by reducing heart rate and myocardial work, could have beneficial effects on energy metabolism and heart function. The reduction of metabolic demand induced by beta-blockade would be beneficial if the myopathic heart cells were deficient in energy-yielding substrates, such as ATP, and at risk of accumulation of metabolites, such as lactate and $NADH^+$. Metabolic overactivity in the myopathic cells could be caused by inappropriately high sympathetic activity or increased sensitivity of the cells to sympathetic stimulation. The delayed clinical deterioration in some patients could be related to structural changes within the myopathic heart cells in the absence of the protective effects of beta-blockade. It is known that catecholamines have a direct stimulatory effect on processes of protein synthesis in the heart, and it has been suggested that the synthesis of a defective contractile protein could be a consequence of increased sensitivity to $beta_1$-stimulation.[7] It seems unlikely that a rebound phenomenon after withdrawal of beta-blockade was of importance in this study. In dogs, haemodynamic and metabolic responses to abrupt withdrawal of beta-blockade usually appear within 24 to 48 hours,[8] and in man it has been reported that the greatest sensitivity to catecholamines after withdrawal of long-term beta-blockade occurs within four to six days.[9] Symptoms such as chest pain and ventricular arrhythmias in patients with ischaemic heart disease have been reported as occurring immediately after chronic treatment is stopped.[10]

In conclusion, the present study strongly supports the hypothesis that sympathetic nervous activity, in some way, plays a role in the development of congestive cardiomyopathy. Any group of patients with congestive cardiomyopathy is heterogeneous and the role of catecholamines in the development of the disease and the appearance of symptoms may be variable. Chronic beta-blockade will produce clinical improvement in some patients but not in others.[3] Similarly, withdrawal of beta-blockade caused a distinct deterioration in some of the patients in this study, but had little influence on the others.

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References

[1] Waagstein F, Hjalmarson Å, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br Heart J* 1975; **37:** 1022–36.

[2] Swedberg K, Hjalmarson Å, Waagstein F, Wallentin I. Prolongation of survival in congestive cardiomyopathy by beta-receptor blockade. *Lancet* 1979; **1:** 1374–6.

[3] Swedberg K, Hjalmarson Å, Waagstein F, Wallentin I. Beneficial effects of long-term beta-blockade in congestive cardiomyopathy. *Br Heart J* 1980; **44:** 117–33.

[4] Chidsey CA, Braunwald E, Morrow AG. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. *Am J Med* 1965; **39:** 442–51.

[5] Johnsson G, Jordö L, Lundborg P, Rönn O, Welin-Fogelberg I, Wikstrand J. Haemodynamic and tolerance studies in man with a new, orally active, selective $beta_1$-adrenoceptor agonist H80/62. *Eur J Clin Pharmacol* 1978; **13:** 163–70.

[6] Ariniego R, Waagstein F, Mombay B, Hjalmarson Å. Haemodynamic effects of a new β_1-receptor agonist in acute myocardial infarction. A useful antidote to unwanted cardiac effects of β-blocking agents. *Br Heart J* 1979; **42:** 139–46.

[7] Källfelt BJ, Hjalmarson ÅC, Isaksson OG. In vitro effects of catecholamines on protein synthesis in perfused rat heart. *J Mol Cell Cardiol* 1976; **8:** 787–802.

[8] Myers JH, Horwitz CD. Hemodynamic and metabolic response after abrupt withdrawal of propranolol. *Circulation* 1978; **58:** 196–201.

[9] Nattel S, Rangno RE, van Loon G. Mechanism of propranolol withdrawal phenomena. *Circulation* 1979; **59:** 1158–64.

[10] Miller RR, Olson HG, Amsterdam EA, Mason DT. Propranolol-withdrawal rebound phenomenon. Exacerbation of coronary events after abrupt cessation of antianginal therapy. *N Engl J Med* 1975; **293:** 416–8.

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Cardiac tumours: non-invasive detection and assessment by gated cardiac blood pool radionuclide imaging

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SUMMARY Four patients with cardiac tumours were investigated by gated cardiac blood pool radionuclide imaging and echocardiography. Contrast angiocardiography was performed in three of the cases. Two left atrial tumours were detected by all three techniques. In one of these cases echocardiography alone showed additional mitral valve stenosis, but isotope imaging indicated tumour size more accurately. A large septal mass was detected by all three methods. In this patient echocardiography showed evidence of left ventricular outflow obstruction, confirmed at cardiac catheterisation, but gated isotope imaging provided a more detailed assessment of the abnormal cardiac anatomy. In the fourth case gated isotope imaging detected a large right ventricular tumour which had not been identified by echocardiography.

Gated cardiac blood pool isotope imaging is a complementary technique to echocardiography for the non-invasive detection and assessment of cardiac tumours.

Cardiac tumours are rare lesions. Formerly contrast angiography was the only available method to establish the diagnosis. Echocardiography is a sensitive non-invasive technique for the detection of cardiac tumours, particularly in the left atrium[1 2] and gated cardiac blood pool radionuclide imaging has been used as an additional atraumatic method to detect left atrial myxomata.[3 4]

Over a six-month period we have investigated four patients with intracardiac tumours, using gated cardiac blood pool imaging in addition to other techniques. In this report we describe the appearance of these tumours.

Imaging methods

Gated cardiac blood pool images were acquired in each case using an Ohio Nuclear Series 100 scintillation camera and a high resolution, parallel-hole collimator, interfaced to a dedicated mini-computer (Digital Equipment Corporation, Gamma 11). Twenty mCi of technetium-99m labelled autologous red blood cells were injected intravenously and after equilibration of the tracer within the blood pool the camera was positioned over the patient's praecordium. Images were obtained in three or four selected views in each patient. The data were stored as a series of 11 R-wave triggered intervals between each QRS complex to a total of four million counts recorded in approximately five minutes for each view.

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Case reports

CASE 1

A 10-year-old boy was admitted to Guy's Hospital for dermatological investigation. Since birth he had been heavily freckled and both parents were freckled. At 2 years of age two tumours were excised from his neck with a local recurrence five years later. Histology of all three specimens showed myxosarcoma of low-grade malignancy.

There were no cardiovascular symptoms. Physical examination showed a red-haired boy with extensive freckling. Pulse rate was 76 per minute with sinus arrhythmia. Blood pressure was 110/70 mmHg. Mitral pansystolic and mid-diastolic murmurs were present intermittently and varied with posture. The remainder of the examination was normal.

Haemoglobin level and leucocyte count were normal. The erythrocyte sedimentation rate was

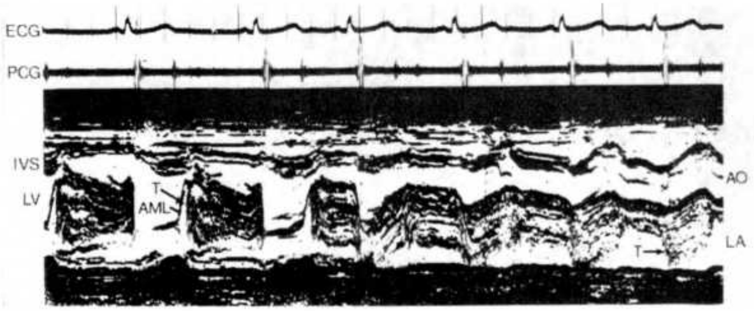

Fig. 1 *Echocardiogram and phonocardiogram (PCG) from case 1. In this sweep from left ventricle (LV) to aorta (AO) the myxoma (T) gives rise to multiple echoes between the mitral leaflets in diastole. In systole the tumour appears to occupy the entire depth of the left atrium (LA). IVS, intraventricular septum; AML, anterior mitral leaflet.*

raised (43 mm/h, Westergren). The electrocardiogram was normal. The chest radiograph showed left atrial enlargement and prominent upper lobe pulmonary vasculature. An echocardiogram showed a tumour which was seen in the left atrium during systole and appeared between the mitral leaflets in diastole (Fig. 1). The echocardiographic appearance of the pulmonary valve suggested pulmonary hypertension. Gated cardiac blood pool images were acquired in four views. The tumour caused a photon-deficient area in the left atrium which moved towards the ventricle in diastole (Fig. 2). Right heart catheterisation confirmed pulmonary hypertension (pulmonary artery pressure 45/20 mmHg). A right ventricular angiogram was normal but follow-through outlined a large left atrial tumour.

At operation a gelatinous tumour occupied the left atrium and bulged through the foramen ovale. A small, separate tumour was attached to the right atrial wall opposite the foramen. Both tumours were removed. Recovery was uneventful. Tumour histology was typical of atrial myxoma. Postoperative echocardiography showed no evidence of residual atrial tumour and normal mitral valve motion.

CASE 2

A 56-year-old woman was transferred to Guy's Hospital with unstable angina pectoris. Inferior myocardial infarction, confirmed by electrocardiogram and enzyme changes, had occurred four months previously and a probable pulmonary infarct occurred a fortnight before transfer. There was a history of malaise, weight loss, and breathlessness for one year, but no history of rheumatic fever.

On arrival the patient appeared ill. She had a regular pulse of 70 per minute with blood pressure 125/85 mmHg. Pansystolic and mid-diastolic murmurs were present. There were signs of pulmonary hypertension and of a left pleural effusion.

Haemoglobin was 11·9 g/dl, with a normal leucocyte count and high erythrocyte sedimentation rate (55 mm/h—Westergren). The electrocardiogram showed sinus rhythm with widespread T wave flattening or inversion, and Q waves in the inferior leads. The chest radiograph showed a left pleural effusion, cardiomegaly, and pulmonary venous congestion. Echocardiography showed an apparently small (1·5 cm depth) left atrial tumour

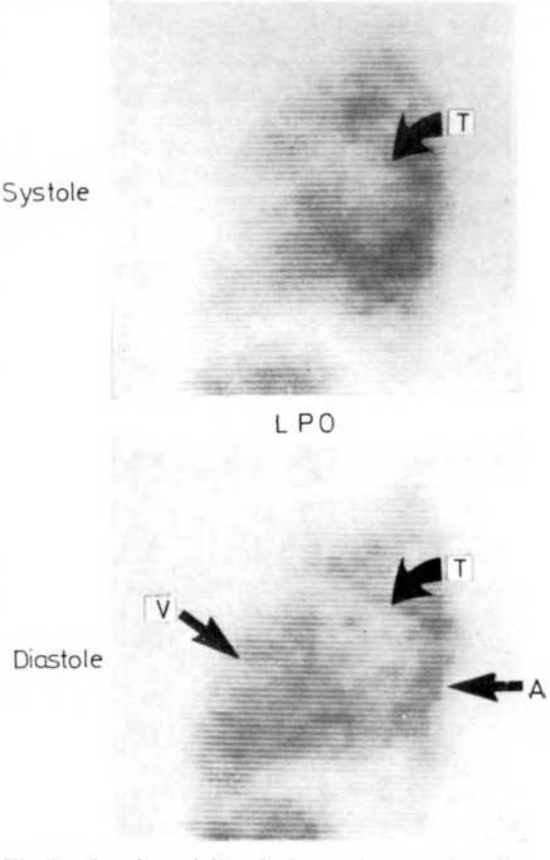

Fig. 2 *Systolic and diastolic images from gated cardiac blood pool study in the left posterior oblique (LPO) projection from case 1. During ventricular systole the myxoma (T) is seen as a photon-deficient area high in the left atrium. In diastole the tumour has moved down to the atrioventricular junction and separates tracer activity in the ventricle (V) from that in atrium (A).*

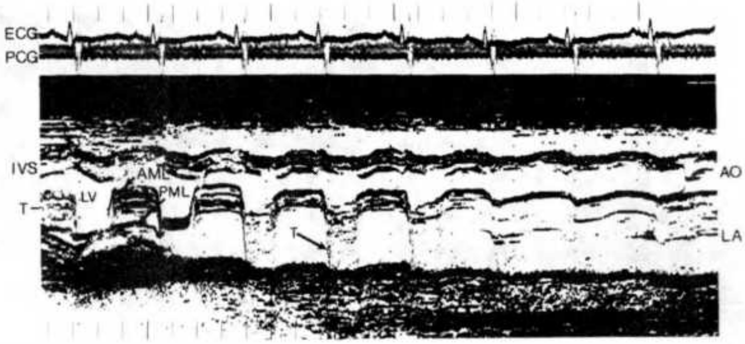

Fig. 3 *Echocardiogram and phonocardiogram (PCG) from case 2. A sweep from left ventricle (LV) to aorta (AO) showing multiple echoes immediately behind the anterior mitral leaflet (AML) in diastole. Echoes from the tumour (T) are also recorded from the left atrium (LA) during systole. In contrast to Fig. 1 the posterior mitral leaflet (PML) moves anteriorly in diastole, indicating additional mitral valve stenosis.*

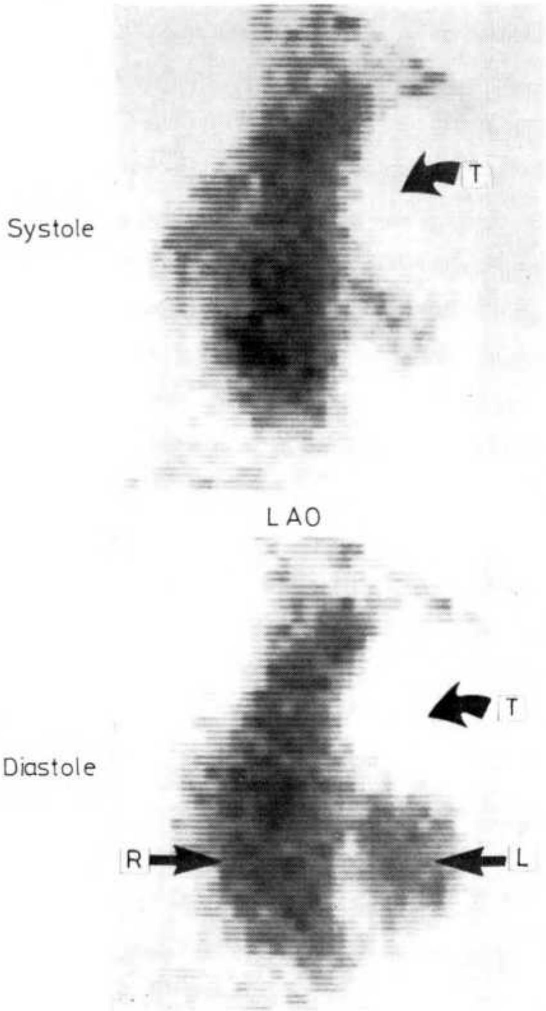

Fig. 4 *Systolic and diastolic gated cardiac blood pool images in the left anterior oblique (LAO) view from case 2. Normal tracer activity is seen in the right ventricle (R) and in the left ventricle (L). However, no tracer activity is recorded from the region of the left atrium which was filled by tumour (T).*

which appeared immediately behind the anterior mitral leaflet in diastole, and moved abruptly into the left atrium in systole. Furthermore, the posterior mitral leaflet echo moved anteriorly in diastole, indicating additional mitral valve stenosis (Fig. 3). The pulmonary valve echogram suggested pulmonary hypertension. Gated cardiac blood pool images showed a large photon-deficient area in the left atrium (Fig. 4). This moved towards the ventricle in diastole. Cardiac catheterisation confirmed pulmonary hypertension (77/35 mmHg, and demonstrated a 22 mmHg end-diastolic gradient between simultaneous pulmonary artery wedge and left ventricular pressures. A left ventricular angiogram showed mitral regurgitation which outlined a large left atrial tumour. This was attached to the anterior mitral leaflet and prolapsed into the ventricle in diastole. Coronary arteriography showed a fistula between the right coronary artery and right atrium and several small vessels to the left atrium suggesting a tumour circulation. The coronary arteries were otherwise normal.

At operation a large tumour (diameter 5 cm) filled the left atrium and was adherent to the anterior mitral cusp. On removing the tumour the mitral valve appeared thickened and mildly stenosed. The postoperative course was complicated by atrial fibrillation. Tumour histology showed a fibrosarcoma. Repeat echocardiography showed no evidence of residual tumour, but the pattern of mitral stenosis persisted (Fig. 5).

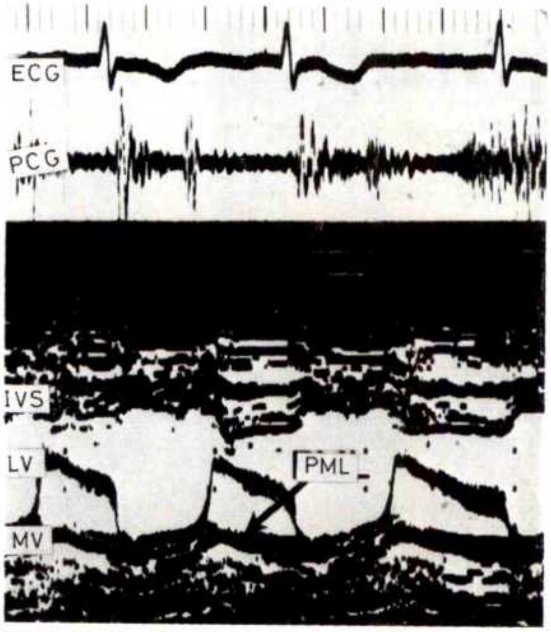

Fig. 5 *Postoperative echocardiogram and phonocardiogram (PCG) from case 2 showing persistence of mild mitral stenosis, indicated by slight anterior motion of the posterior mitral leaflet (PML) in early diastole. MV, mitral valve.*

CASE 3

A 21-year-old Iranian girl was transferred to Guy's Hospital for investigation of suspected pericarditis. She gave a history of increasing sharp praecordial pain, affected by posture and respiration, for three months. Ten years previously a chondrosarcoma, arising in costal cartilage at the left sternal border, had been excised, but until the present illness the patient had remained well, with no sign of recurrence.

On arrival the patient was apyrexial. Pulse rate was 82 per minute, regular, with no paradox. The apex beat was impalpable. A pericardial rub was audible. The remainder of the examination was normal. The electrocardiogram showed reduced voltage in all leads and a chest radiograph showed cardiomegaly. Echocardiography was technically difficult, but confirmed the presence of a large pericardial effusion. Intracardiac structures were poorly defined, and, in particular, definition of the right ventricular/septal endocardium was prevented by the recording of multiple echoes, apparently from within the right ventricular cavity (Fig. 6). Gated cardiac blood pool imaging also showed the pericardial effusion; in addition a region of greatly reduced tracer activity was seen, replacing the activity normally recorded from the right ventricle and much of the right atrium (Fig. 7). Diagnostic pericardial aspiration disclosed lightly bloodstained fluid in which malignant cells were not found on cytological examination. Thereafter the patient elected to defer further investigation or treatment; but she subsequently presented elsewhere with metastatic chondrosarcoma in the leg.

CASE 4

A 4-year-old boy was admitted to hospital for

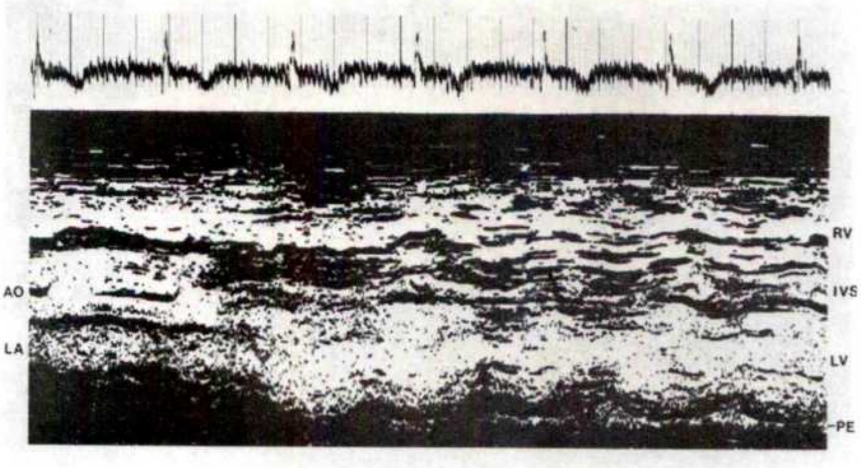

Fig. 6 *Echocardiogram from case 3. A technically difficult study showing a sweep from aorta (AO) and left atrium (LA) to left ventricle (LV). A pericardial effusion (PE) is visible behind the LV, but the effusion is not well seen anteriorly because of the gain setting for this part of the recording. Several echoes are recorded from within the cavity of the right ventricle (RV), obscuring the endocardial echo between RV and septum (IVS).*

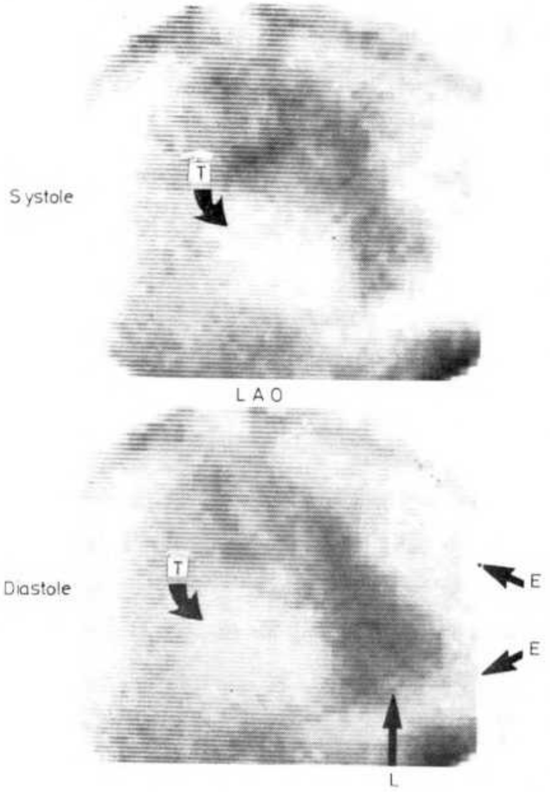

Fig. 7 *Systolic and diastolic images in the left anterior oblique (LAO) view from case 3. An area of reduced tracer activity (T) indicates the presence of tumour within the right ventricle, whereas normal tracer activity is recorded from the left ventricle (L). The intracardiac tracer activity is surrounded by a halo of relatively reduced activity (E) which represents a large pericardial effusion.*

investigation of a heart murmur, first noted by his family doctor at age 2 years. The patient was easily fatigued but his growth and milestone achievement had been normal. There was no other previous medical history and no family history of heart disease.

On examination, height and weight were at the 70th and 75th centiles for age, respectively. The pulse was regular at 92 per minute and of normal character. Blood pressure was 105/60 mmHg. The heart was enlarged, with a sustained left parasternal heave and a basal ejection systolic murmur. The remainder of the examination was normal.

Haematological and biochemical screens were normal. The electrocardiogram showed sinus rhythm with a QRS axis of −120°, complete right bundle-branch block, and pronounced right ventricular hypertrophy. The chest radiograph showed cardiac enlargement. An echocardiogram showed a greatly thickened interventricular septum with reduced motion. Motion of the posterior wall was increased. There was systolic anterior motion of the mitral valve, suggesting left ventricular outflow obstruction but the aortic valve appeared normal (Fig. 8). Pronounced septal hypertrophy was also seen on the gated cardiac blood pool images which also showed increased thickness of the free wall and apex of the left ventricle (Fig. 9). Cardiac catheterisation demonstrated a systolic pressure gradient of 20 mmHg across the left ventricular outflow tract. Intracardiac pressures were otherwise normal. A right ventricular angiogram showed a large mass protruding from the septum into the right ventricle; left ventriculography showed a septal mass encroaching on the left ventricular outflow tract, and hypertrophied papillary muscles.

At operation a large purple mass occupied the upper septum and appeared to extend into the free

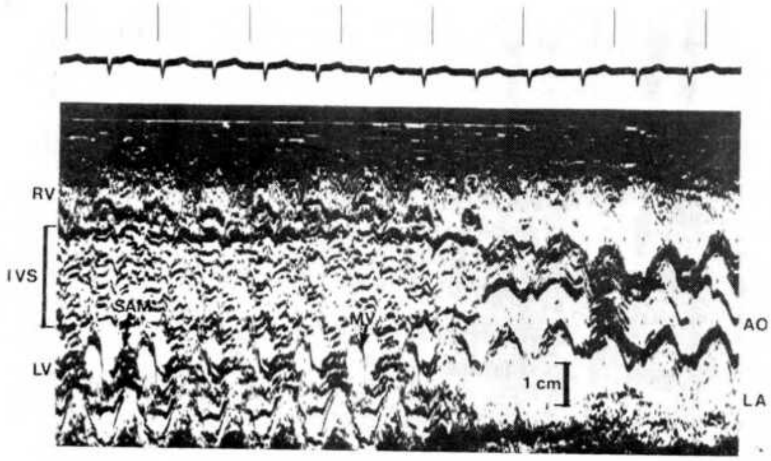

Fig. 8 *Echocardiogram from case 4; sweep from the left ventricle (LV) to aorta (AO) and left atrium (LA). The septum (IVS) is greatly thickened and is hypokinetic. The mitral valve (MV) shows systolic anterior motion (SAM) indicating LV outflow obstruction.*

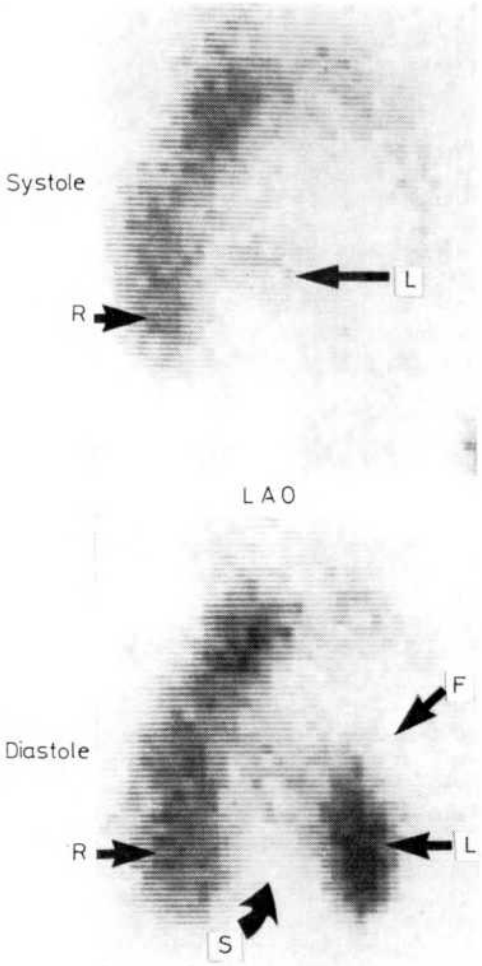

Fig. 9 *Systolic and diastolic left anterior oblique gated images from case 4. In diastole normal tracer activity is seen in the right ventricle (R) and left ventricle (L), separated by a wide band of low activity indicating a thickened septum (S). A halo of relatively low tracer activity around the remainder of the left ventricle suggests hypertrophy of the free wall (F). In systole, left ventricular tracer activity is almost obliterated.*

wall of the left ventricle. As resection was not feasible a biopsy was taken and the heart was closed again. Histology showed hypertrophied cardiac muscle with no evidence of neoplasia and no myocardial fibre disarray. Postoperative recovery was uneventful.

Both parents have had clinical examinations, electrocardiograms, and echocardiograms, all of which were normal.

Discussion

Because of the rarity of cardiac tumours and their wide spectrum of non-specific manifestations,[5] well illustrated by these four cases, atraumatic techniques which allow detection of these lesions have an important place in the investigation of patients with unexplained cardiac symptoms or signs, so that potentially resectable lesions may be detected early. Gated cardiac blood pool imaging is such a technique. Intracavity cardiac tumours may be seen as filling defects within any of the cardiac chambers, and their motion may be demonstrated, as in our first three cases. Thickening of the myocardium (by tumour or hypertrophy) may also be detected by this method, particularly when this involves the interventricular septum, as in hypertrophic cardiomyopathy.[6] Hence the widening of the septum was easily detected in the left anterior oblique view in case 4.

In our first two cases echocardiography identified the presence of the tumours and demonstrated their motion. In case 1 little additional information was gained from the gated images; in case 2 gated radionuclide imaging gave a more accurate indication of tumour size, whereas the echocardiogram alone detected mitral valve stenosis. The ability to obtain two-dimensional images in multiple views in case 4 allowed the extent of left ventricular hypertrophy to be defined much more precisely than by single-beam echocardiography. The echocardiogram, on the other hand, detected evidence of left ventricular outflow obstruction which was otherwise demonstrated only by cardiac catheterisation. Neither echocardiography nor gated isotope imaging provided a firm diagnosis in this case, and though the angiogram suggested a septal tumour, operative biopsy also failed to distinguish neoplasm from hypertrophic cardiomyopathy. Finally, in case 3, the echocardiogram was technically difficult. The presence of a pericardial effusion was confirmed, but the tumour was not clearly identified and merely gave rise to non-specific echoes within the right ventricle, obscuring the septal endocardium. In contrast, the gated cardiac blood pool images clearly showed a large photon-deficient area within the right ventricle, together with the large pericardial effusion.

As in this last example, echocardiography is technically difficult or impossible in a small proportion of subjects,[7] and occasionally cardiac tumours are not detected by ultrasound despite adequate recordings.[8] Pohost *et al.*[4] failed to diagnose two out of seven left atrial myxomata by echocardiography, and one out of seven was not detected on gated images. These authors suggest that this latter failure was the result of multiple lobulation of the myxoma, allowing the passage of blood between the lobules and resulting in the recording of tracer activity from the region occupied by the tumour. It is just this type of tumour in which multiple surfaces might be expected to give rise to multiple ultrasonic echoes, which allow easy echocardiographic diagnosis. Conversely, a solid tumour of uniform density may be less easy to detect by echocardiography and more readily identified by isotope imaging.

Thus gated cardiac blood pool radionuclide imaging appears to be complementary to echocardiography for the atraumatic detection and assessment of cardiac tumours. It appears to be of particular diagnostic value in patients in whom echocardiography is technically difficult or non-diagnostic. The demonstration of a cardiac tumour by either of these techniques may permit surgical exploration without the need for cardiac catheterisation and contrast angiography.

References

1 Schattenberg TT. Echocardiographic diagnosis of left atrial myxoma. *Mayo Clin Proc* 1968; **61:** 620–7.
2 Wolfe SB, Popp RL, Feigenbaum H. Diagnosis of atrial tumors by ultrasound. *Circulation* 1969; **39:** 615–22.
3 Bonte FJ, Curry TS. Technetium-99m HSA blood pool scan in diagnosis of an intracardiac myxoma. *J Nucl Med* 1969; **8:** 35–9.
4 Pohost GM, Pastore JO, McKusick KA, *et al.* Detection of left atrial myxoma by gated radionuclide cardiac imaging. *Circulation* 1977; **55:** 88–92.
5 Selzer A, Sakai FJ, Popper RW. Protean clinical manifestations of primary tumors of the heart. *Am J Med* 1972; **52:** 9–18.
6 Pohost GM, Vignola PA, McKusick KA, *et al.* Hypertrophic cardiomyopathy. Evaluation by gated cardiac blood pool scanning. *Circulation* 1977; **55:** 92–9.
7 Gramiak R. Echocardiography in acquired heart disease. In: King DL, ed. *Diagnostic ultrasound.* St Louis: CV Mosby, 1974: 84.
8 Guiliani ER, Lemire F, Schattenberg TT. Unusual echocardiographic findings in a patient with left atrial myxoma. *Mayo Clin Proc* 1978; **53:** 469–72.

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Prediction of mortality and serious ventricular arrhythmia in hypertrophic cardiomyopathy

An echocardiographic study

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SUMMARY M-mode echocardiography was performed on 26 patients with clinical and angiographic hypertrophic cardiomyopathy to assess the echocardiographic prediction of serious ventricular arrhythmia. These patients had previously undergone 48-hour ambulatory electrocardiographic monitoring both on and off beta-adrenergic blocking drugs and were grouped according to the most serious ventricular arrhythmia detected: (A) ventricular tachycardia, eight patients; (B) multiform or paired ventricular extrasystoles, 11 patients; (C) uniform ventricular extrasystoles, seven patients. Septal amplitude of motion at chordal level and septal systolic thickening showed a significant difference between group A and C, and group B and C. Systolic anterior movement of the mitral valve and mid-systolic closure of the aortic valve were detected with identical frequency and were both seen in two patients (25%) in group A, seven patients (64%) in group B, and six patients (86%) in group C. These echocardiographic features of obstruction were inversely correlated with ventricular tachycardia. Septal amplitude of motion was then assessed just below the mitral valve and at chordal level by continuous sweep recording and the pattern of septal motion was graded from normal (type I) to absent (type V) or as paradoxical (type VI). Six patients (75%) in group A showed type IV, V, or VI; seven patients (64%) in group B showed type III; and six patients (86%) in group C showed type I or II. The patients with ventricular tachycardia were the patients with the most severely impaired pattern of septal motion.

Sudden death is the most important feature of the natural history of hypertrophic cardiomyopathy since it is often unexpected and is the commonest mode of death.[1] The recent detection of a 50 per cent incidence of serious ventricular arrhythmia in an unselected series of patients with hypertrophic cardiomyopathy may have provided a valuable predictor of those patients at particular risk.[2] No clinical or haemodynamic index predicted which of those patients would have ventricular tachycardia, and this is consistent with retrospective studies which have failed to identify predictive features for sudden death.[3]

Although not proven, patients with serious ventricular arrhythmia are likely to be at risk from sudden death. This study was undertaken to examine the M-mode echocardiogram for features predictive of serious ventricular arrhythmia. In addition to the classical echocardiographic features, special attention has been focused on a continuous sweep recording from the base of the heart longitudinally toward the apex to assess amplitude of motion at different levels of the ventricular septum.

Subjects and methods

M-mode echocardiography was performed on 26 of 27 unselected patients with clinical and angiographic evidence of hypertrophic cardiomyopathy who had previously undergone 48-hour outpatient ambulatory electrocardiographic monitoring both off and on beta-adrenergic blocking drugs.[2] The echocardiography was performed one to nine months (mean: three months) from the ambulatory

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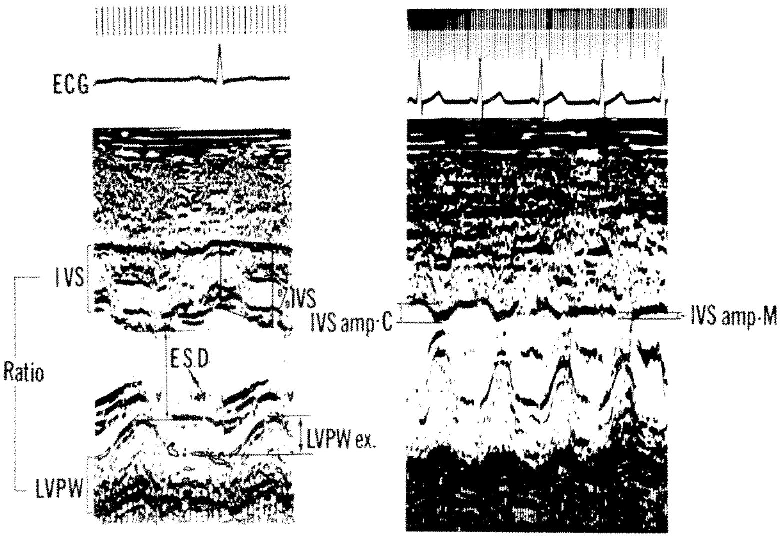

Fig. 1 *The echocardiographic features assessed. ECG, electrocardiogram; IVS, ventricular septal thickness; Ratio, ventricular septal thickness to posterior wall ratio; ESD, end-systolic dimension; % IVS, septal systolic thickening; LVPW ex, left ventricular posterior wall excursion; IVS amp-C, ventricular septal amplitude of motion at chordal level; IVS amp-M, ventricular septal amplitude of motion just below mitral valve level.*

lectrocardiographic monitoring. All of these 26 patients had undergone cardiac catheterisation within the three years before this study and were on beta-adrenergic blocking drugs (range in propranolol equivalents: 60 to 800 mg, mean: 260 mg/day) when they were studied by echocardiography.

Fifteen patients were men and 11 were women. The mean age was 48 years (age range: 21 to 71). Twenty-one of the patients were in sinus rhythm and five in established atrial fibrillation. Twelve of the patients complained of palpitation and six of these patients had had at least one previous episode of syncope.

Left ventricular, mitral valve leaflet, aortic root, and left atrial echocardiograms and continuous sweep recordings of the ventricular septum from the base of the heart toward the apex were obtained by standard methods.[4] Ekoline 20 Ultrasonoscope was used with a 2·25 MHz transducer and a repetition frequency of 1000 pulses/s. The output was displayed on the Cambridge strip chart recorder with a simultaneous electrocardiogram. Studies were made with patients in the supine or slight left lateral position, with the transducer at the left sternal edge.

The following echocardiographic features were assessed (Fig. 1 and 2): (1) ventricular septal amplitude of motion; (2) ventricular systolic septal thickening; (3) ventricular septal thickness at end-

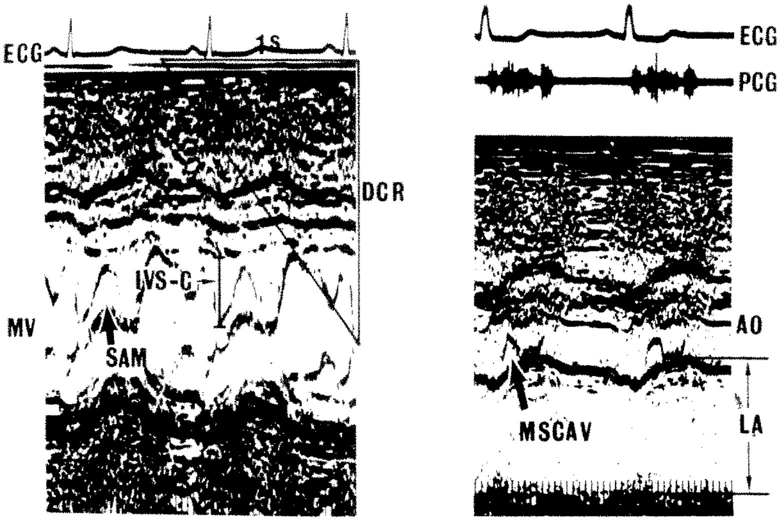

Fig. 2 *The echocardiographic features assessed. MV, mitral valve; IVS-C, septal mitral valve distance at the onset of systole; SAM, systolic anterior movement of the mitral valve; DCR, diastolic closure rate of the anterior mitral valve; MSCAV, mid-systolic closure of the aortic valve; AO, aortic root; LA, left atrial dimension.*

PATTERN OF VENTRICULAR SEPTAL MOTION

TYPE	Just below (or at) MV level	At Chordal level
I	Normal	Normal
II	Reduced	Normal
III	Reduced	Reduced
IV	Flat	Reduced
V	Flat	Flat
VI	Paradoxical	Paradoxical

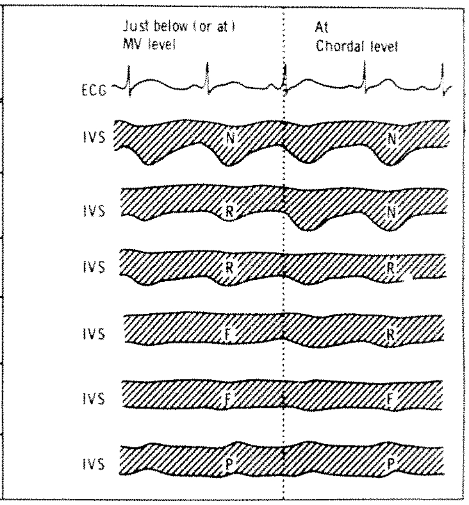

Fig. 3 *Six types of septal motion. N, normal septal motion (amplitude of motion > 5 mm); R, reduced septal motion (5 to 3 mm); F, flat septal motion (2 to 0 mm); P, paradoxical septal motion; MV, mitral valve; IVS, ventricular septum; "Flat" (at MV level) + "paradoxical" (at chordal level) is theoretically possible but not detected in these 26 patients.*

diastole; (4) ventricular septal thickness to left ventricular posterior wall ratio; (5) left ventricular posterior wall excursion; (6) left ventricular end-systolic dimension; (7) septal mitral valve distance at the onset of systole; (8) diastolic closure rate of the anterior mitral valve leaflet; (9) systolic anterior movement of the mitral valve; (10) mid-systolic closure of the aortic valve; (11) left atrial dimension at end-systole. Ventricular septal amplitude of motion (Fig. 1) was assessed just below (or at) the plane of the mitral valve and at chordal level by continuous sweep recording of the ventricular septum from the base toward the apex, and the pattern of septal motion seen was classified into six types based on normal, reduced, flat, or paradoxical septal motion (Fig. 3). Features (2) to (6) were assessed from the echocardiograms obtained just below the plane of the mitral valve, where the minor axis of the left ventricle was recorded (Fig. 1). Feature (2) septal systolic thickening was expressed as systolic thickness minus diastolic thickness divided by diastolic thickness (S–D/D). Features (7) to (9) were assessed from the echocardiograms obtained at the plane of the mitral valve tip where both anterior and posterior leaflets were recorded simultaneously (Fig. 2). Features (10) and (11) were assessed from the echocardiograms obtained at the plane of the aortic root and the left atrium where both anterior and posterior aortic cusps were visualised (Fig. 2).

The arrhythmias detected have been reported elsewhere.[2] The frequency of ventricular tachycardia was almost identical with or without beta-adrenergic blocking drugs. For the purpose of this study the patients were grouped according to the most serious ventricular arrhythmia present with or without beta-adrenergic blocking drugs: group (A) ventricular tachycardia defined as three or more

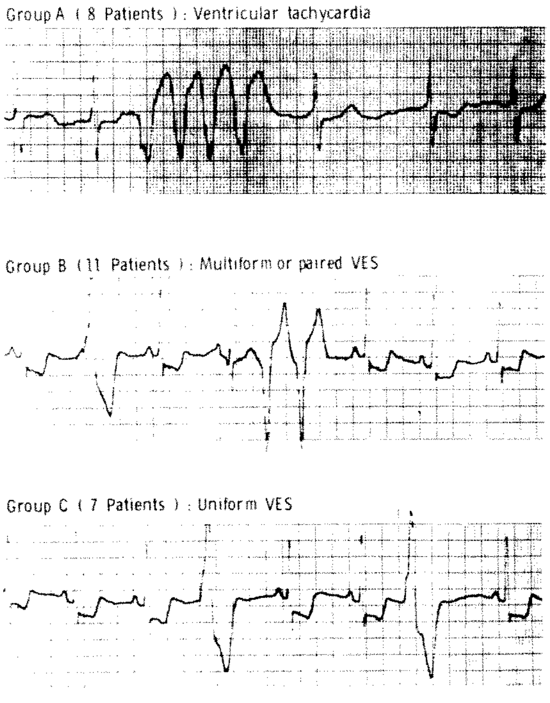
Group A (8 Patients) : Ventricular tachycardia
Group B (11 Patients) : Multiform or paired VES
Group C (7 Patients) : Uniform VES

Fig. 4 *Representative ambulatory electrocardiograms in three groups of patients. VES, ventricular extrasystoles.*

ventricular extrasystoles in succession, eight patients; group (B) multiform or paired ventricular extrasystoles, 11 patients; group (C) uniform ventricular extrasystoles, seven patients (Fig. 4). In group (C), five patients had fewer than 30 ventricular extrasystoles an hour and two patients had more than 30 ventricular extrasystoles an hour. The echocardiographic features assessed were compared in these groups.

Standard statistical analyses were performed. The difference between two proportions was examined using the Fisher's exact test. One-way analysis of variance was performed initially to test the difference between means of more than two groups and this was followed by a two-sample t test when the result was significant.

Results

Results are shown in the Table.

Mean ventricular septal amplitude of motion at chordal level was 4·0 ±0·9 (standard error of the mean) mm in group A, 5·5 ±0·4 mm in group B, and 7·0 ±0·6 mm in group C, and there was a significant difference between group A and C (p=0·017), group B and C (p=0·042), and group A+B and C (p=0·015), but no significant difference between group A and B (Fig. 5).

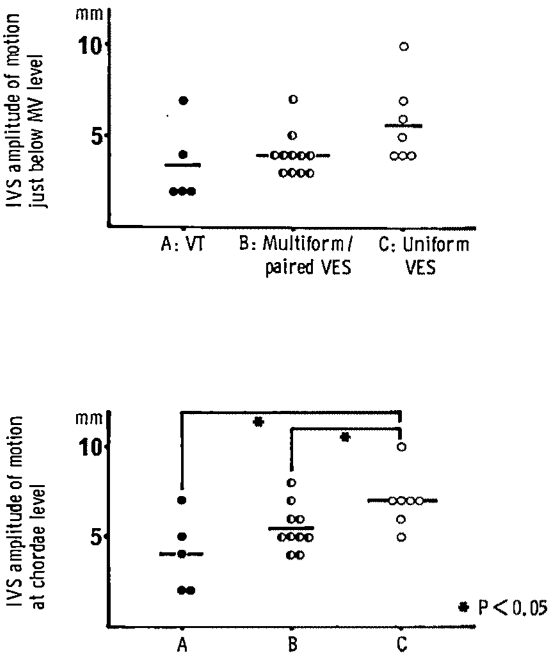

Fig. 5 *Ventricular septal amplitude of motion. IVS, ventricular septum; MV, mitral valve; VT, ventricular tachycardia; VES, ventricular extrasystoles.*

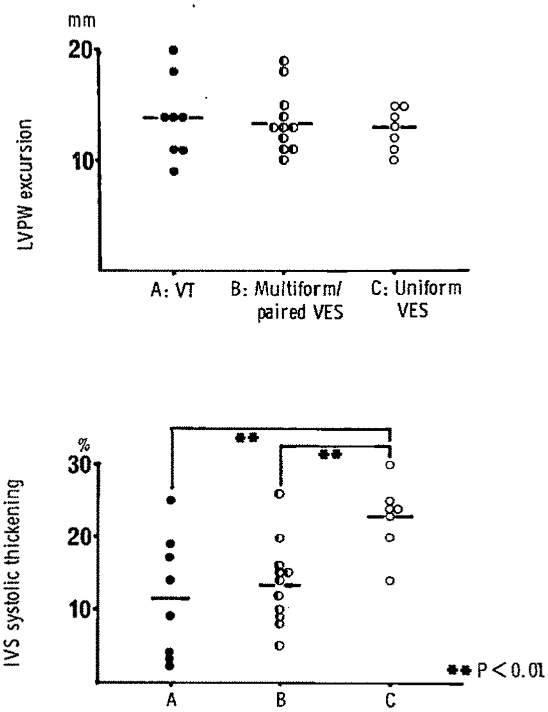

Fig. 6 *Left ventricular posterior wall excursion and ventricular septal systolic thickening. VT, ventricular tachycardia; VES, ventricular extrasystoles.*

Mean septal systolic thickening was 11·6 ±3·0 per cent in group A, 13·6 ±1·8 per cent in group B, and 22·9 ±1·9 per cent in group C. There was significant difference between group A and C, group B and C, and group A+B and C (p <0·01 for each), but no significant difference between group A and B (Fig. 6). Mean ventricular septal amplitude of motion just below the mitral valve level, left ventricular posterior wall excursion, ventricular septal thickness, or ventricular septal thickness to posterior wall ratio did not show any significant difference in these three groups of patients.

Within each group systolic anterior movement of the mitral valve and mid-systolic closure of the aortic valve were detected with identical frequency: two patients (25%) in group A, seven patients (64%) in group B, and six patients (86%) in group C, and there was a significant difference between group A and C (p <0·05) (Fig. 7).

Six different patterns of septal motion were derived from the amplitude of septal motion at two different levels: just below the plane of the mitral valve and at chordal level. In group A, six of eight patients (75%) showed type IV, V, or VI. In group B, seven of 11 patients (64%) showed type III. In group C, six of seven patients (86%) showed type I or II (Fig. 3 and 8).

Three patients had paradoxical septal motion (type VI), and since completion of the study two of them have died. Case 1 was diagnosed in 1973. He was in left ventricular failure, on digitalis and diuretics, and died suddenly. His echocardiogram showed paradoxical septal motion and decreased septal systolic thickening. Case 2 was operated on in 1958 and was the first patient to be treated surgically. Apart from a syncopal episode, he was in controlled left ventricular failure, but died suddenly while watching television. His electrocardiogram showed left bundle-branch block and his echocardiogram showed a grossly thickened septum with paradoxical septal motion and reduced septal systolic thickening. He was the only patient in the study with bundle-branch block. The other two patients with paradoxical septal motion had no clinical or echocardiographic evidence of other causes of paradoxical septal motion.

Discussion

None of the classical echocardiographic features of hypertrophic cardiomyopathy was predictive of serious ventricular arrhythmia, except ventricular septal amplitude of motion and septal systolic thickening. Though the echocardiographic features of obstruction, systolic anterior movement of the mitral valve and mid-systolic closure of the aortic valve,[5–7] had previously been positively associated with ventricular arrhythmia,[8] we found the oppo-

Table *Echocardiographic data in group A : ventricular tachycardia in group B : multiform or paired ventricular extrasystoles, and in group C : uniform ventricular extrasystoles*

Case no.	*Sex*	*Age (y)*	*Pattern of IVS motion*	*IVS amplitude (mm)*		*IVS systolic thickening (%)*	*IVS thickness (mm)*	*IVS/ LVPW ratio*	*LVPW excursion (mm)*	*LVESD (mm)*	*IVS-C (mm)*	*DCR (mm/s)*
				Just below MV level	*At chordae level*							
Group A												
1	M	59	VI	(P)	(P)	14	19	1·9	11	43	19	43
2	M	62	VI	(P)	(P)	2	29	4·8	14	24	10	22
3	M	44	VI	(P)	(P)	9	20	2·5	18	30	32	60
4	M	49	III	4	4	19	22	2·2	9	26	19	16
5	M	56	V	2	2	3	29	3·6	14	34	27	136
6	F	57	I	7	7	25	14	1·6	11	21	21	91
7	F	37	IV	2	5	17	20	1·6	14	17	27	58
8	M	37	V	2	2	4	27	1·9	20	18	25	19
Mean				3·4	4·0	11·6	22·5	2·5	13·9	26·6	22·5	55·6
±SEM				±1·0	±0·9	±3·0	±1·9	±0·4	±1·3	±3·1	±2·4	±14·6
Group B												
9	M	23		3	—	9	11	1·6	11	36	23	72
10	F	57	III	4	5	8	25	1·0	11	21	19	16
11	M	35	I	7	7	20	15	0·9	15	17	22	17
12	M	44	II	5	6	15	20	1·8	10	25	26	30
13	M	58	III	4	4	10	22	1·7	13	27	24	41
14	F	60	II	4	6	15	23	2·3	12	19	19	35
15	F	59	III	4	4	5	23	2·3	19	31	22	74
16	F	71	III	3	5	14	20	1·8	13	26	24	88
17	M	32	III	3	5	26	17	1·9	14	14	19	21
18	M	43	III	3	5	16	21	2·6	18	22	24	45
19	F	55	II	4	8	12	17	1·9	13	24	27	51
Mean				4·0	5·5	13·6	19·5	1·8	13·6	23·8	22·6	44·6
±SEM				±0·4	±0·4	±1·8	±1·2	±0·2	±0·9	±1·9	±0·8	±7·4
Group C												
20	F	51	II	4	7	24	19	2·7	11	21	15	—
21	M	60	I	7	7	24	28	3·1	14	24	25	0
22	F	59	III	4	5	14	20	2·2	15	24	25	35
23	M	48	I	10	10	20	27	1·4	13	19	25	13
24	M	44	I	6	7	23	15	1·4	12	24	18	183
25	F	31	II	5	7	30	21	1·9	15	26	18	0
26	F	21	II	4	6	25	12	1·3	10	29	31	63
Mean				5·7	7·0	22·9	20·3	2·0	12·9	23·9	22·4	49·0
±SEM				±0·8	±0·6	±1·9	±2·2	±0·3	±0·7	±1·2	±2·1	±28·6

IVS, interventricular septum; MV, mitral valve; LVPW, left ventricular posterior wall; ESD, end-systolic dimension; IVS-C, septal-mitral valve distance; DCR, diastolic closure rate of the mitral valve; SAM, systolic anterior movement of the mitral valve; MSCAV, mid-systolic closure of the aortic valve; LA, left atrium; (P), paradoxical septal motion; LBBB, left bundle-branch block; SR, sinus rhythm; AF, atrial fibrillation; LVH, left ventricular hypertrophy EDP, end-diastolic pressure; NON, non-obstructive; L, labile obstructive; R, resting obstructive.

site. In our study the presence of systolic anterior movement of the mitral valve and/or mid-systolic closure of the aortic valve were inversely correlated with ventricular tachycardia (Fig. 7). This is consistent with our natural history study in which an overall worse prognosis was found in the patient who had no resting or provokable gradient at the follow-up haemodynamic study.[9]

It has been previously postulated that loss of outflow tract obstruction may be associated with impairment of contractile function and may indicate progression of the disease.[10] This concept was supported by previous histological studies where the typical findings of the alteration in the shape of the muscle cells and the abnormalities of myofibrillar structure and orientation are present in the ventricular septum,[11] but are either absent or rarely found in muscle from the left and right ventricular free walls in the patients with obstruction. In contrast, many abnormal cells were extensively present in the left and right ventricular free walls in seven of eight patients without obstruction,[12] suggesting that extensive involvement of the free walls of the ventricles as well as the septum is limited to the patients without obstruction. Our result that echocardiographic features of obstruction were inversely correlated with ventricular tachycardia and risk of sudden death fits in with this concept that patients with gradients have more circumscribed and less widespread disease than those without obstruction.

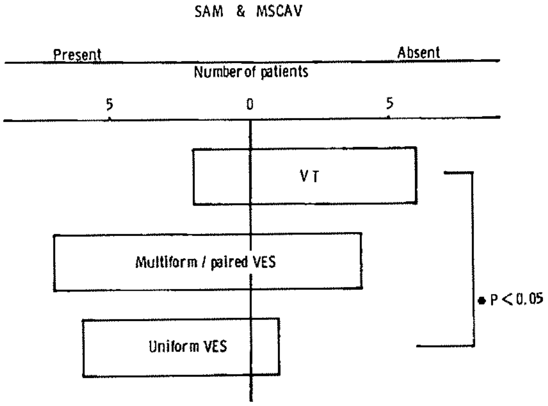

Fig. 7 *Systolic anterior movement of the mitral valve (SAM) and mid-systolic closure of the aortic valve (MSCAV). VT, ventricular tachycardia; VES, ventricular extrasystoles.*

SAM/ MSCAV	*LA (mm)*	*Mean VCF*	*ECG*	*LVEDP (mmHg)*	*LV gradient*
-/-	64	0·5	AF,LVH	32	L
-/-	29	1·3	SR,LBBB	20	L
-/-	28	1·1	SR	—	L
+/+	50	0·9	SR,LVH	16	R
-/-	53	0·7	SR	15	NON
-/-	38	1·4	SR	15	L
-/-	27	1·3	SR,LVH	28	NON
+/+	33	1·4	SR,LVH	36	R
	40·3 ±4·9	1·1 ±0·1		23·1 ±3·3	
-/-	45	—	SR,LVH	20	NON
+/+	31	1·4	SR	15	L
+/+	49	1·8	SR,LVH	20	L
-/-	34	0·8	SR	24	NON
+/+	27	1·2	SR,LVH	—	L
+/+	39	1·4	SR,LVH	18	R
+/+	50	1·2	SR	25	R
-/-	40	1·0	SR,LVH	20	NON
-/+	34	1·4	SR,LVH	16	L
-/-	34	1·1	SR,LVH	—	NON
-/+	40	1·0	SR,LVH	24	L
	38·5 ±2·2	1·2 ±0·9		20·2 ±1·2	
-/+	39	1·2	SR	20	L
-/+	27	1·3	SR,LVH	20	R
-/-	50	1·2	AF	—	L
-/+	60	1·7	SR,LVH	20	L
-/+	53	1·1	AF,LVH	16	R
-/+	44	1 4	SR	19	R
-/+	32	0·7	SR,LVH	12	R
	43·6 ±4·4	1·2 ±0·1		17·8 ±1·3	

In this study there was no correlation between serious ventricular arrhythmia and ventricular

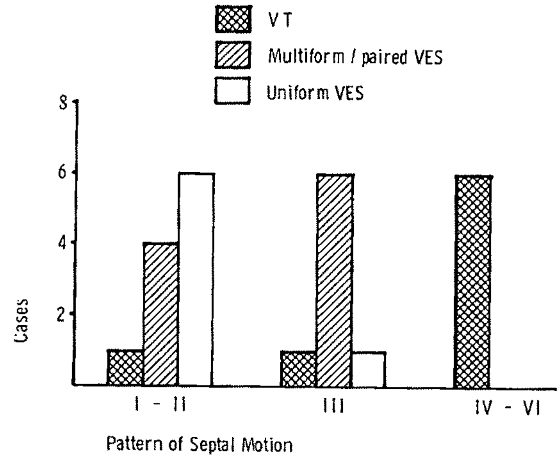

Fig. 8 *Type of septal motion seen in the three groups of patients. VT, ventricular tachycardia; VES, ventricular extrasystoles.*

septal thickness. Ventricular septal systolic thickening just below the plane of the mitral valve and the septal amplitude of motion at chordal level best correlated, however, with serious ventricular arrhythmia. Assessment of the ventricular septal amplitude of motion at one level can provide only limited information about the overall function and degree of involvement of the ventricular septum. The changes in septal motion at different levels in hypertrophic cardiomyopathy recorded by a continuous sweep from the base towards the apex have previously been demonstrated.[13] The septal amplitude of motion and systolic septal thickening have been studied by several investigators,[13–15] but none has previously attempted to assess septal motion at different levels. Histologically, the ventricular septum is the part of the heart which is most frequently involved and which shows the most severe changes and that is why we examined the whole length of the septum in order to describe its function *in toto* and not just at one site. The septal amplitude of motion was measured just below mitral valve level and at chordal level. Six different patterns of septal motion could be described (Fig. 3 and 8): 86 per cent of patients without serious ventricular arrhythmia showed normal (type I) or nearly normal (type II) patterns of septal motion, whereas severely impaired septal motion at both levels (type IV, V, and VI) was present in 75 per cent of the patients with ventricular tachycardia; 64 per cent of patients with serious ventricular arrhythmia showed moderately impaired septal motion (type III).

Paradoxical septal motion (type VI) appears to indicate the most severe form of ventricular septal dysfunction. It was found only in three patients; two have died suddenly and all three had ventricular tachycardia (Table: cases 1 to 3). The echocardiograms of the patients with ventricular tachycardia showed features of severity; (1) decreased septal amplitude of motion or paradoxical motion progressively along the septum from the base toward the apex; (2) conspicuously decreased septal systolic thickening.

Precise electrophysiological studies on these patients have not been performed and we are unable to determine the origin of the ventricular tachycardia from ambulatory electrocardiographic monitoring. Theoretically, extensive involvement of the ventricular septum by the myopathic process will provide an ideal locale for the initiation of re-entry circuits, but this remains to be investigated.

In conclusion, two indicators of ventricular septal function, amplitude of motion at chordal level and septal systolic thickening, best predicted serious ventricular arrhythmia. Two of three patients who had paradoxical septal motion died suddenly, but because of the presence of possible other explanations for paradoxical septal motion we hesitated to emphasise this correlation between paradoxical septal motion and sudden death. Additional information was obtained by a continuous sweep recording of the septum from the base toward the apex. This provided further assessment of septal function. The echocardiographic features of obstruction, systolic anterior movement of the mitral valve and mid-systolic closure of the aortic valve, were inversely correlated with ventricular tachycardia.

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References

1 Hardarson T, De La Calzada CS, Curiel R, Goodwin JF. Prognosis and mortality of hypertrophic obstructive cardiomyopathy. *Lancet* 1973; **ii:** 1462–7.

2 McKenna WJ, Chetty S, Oakley CM, Goodwin JF. Arrythmia in hypertrophic cardiomyopathy: exercise and 48 hour ambulatory electrocardiographic assessment with and without beta adrenergic blocking therapy. *Am J Cardiol* 1980; **45:** 1–5.

3 Maron BJ, Roberts WC, Edwards JE, McAllister HA, Foley DD, Epstein SE. Sudden death in patients with hypertrophic cardiomyopathy: characterisation of 26 patients without functional limitation. *Am J Cardiol* 1978; **41:** 803–10.

4 Feigenbaum H. Clinical application of echocardiography. *Progr Cardiovasc Dis* 1972; **14:** 531–58.

5 Shah PM, Gramiak R, Kramer DH. Ultrasound localization of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy. *Circulation* 1969; **40:** 3–11.

6 Gramiak R, Shah PM, Kramer DH. Ultrasound cardiology; contrast studies in anatomy and function. *Radiology* 1969; **92:** 939–48.

7 Doi YL, McKenna WJ, Gehrke J, Oakley CM, Goodwin JF. M-mode echocardiography in hypertrophic cardiomyopathy; diagnostic criteria and prediction of obstruction. *Am J Cardiol* 1980; **45:** 6–14.

8 Lever HM, Shah PM, Reeves WC, Nanda NC, Gramiak R. The relation of left ventricular outflow obstruction to ventricular arrhythmias in hypertrophic subaortic stenosis (abstract). *Circulation* 1976; **53 & 54,** suppl II: 105.

9 McKenna WJ, Deanfield J, Oakley CM, Goodwin JF. Prognosis and mortality in hypertrophic cardiomyopathy (abstract). *Circulation* 1979; **59** & **60,** suppl II: 164.

10 Goodwin JF, ? IHSS, ? HOCM, ? ASH. A plea for unity. *Am Heart J* 1975; **89:** 269–77.

11 Ferrans VJ, Morrow AG, Roberts WC. Myocardial ultrastructure in idiopathic hypertrophic subaortic stenosis; study of operatively excised left ventricular

outflow tract muscle in 14 patients. *Circulation* 1972; **45:** 769–92.
12 Maron BJ, Ferrans VJ, Hentry WL, *et al.* Differences in distribution of myocardial abnormalities in patients with obstructive and nonobstructive asymmetric septal hypertrophy (ASH); light and electron microscopic findings. *Circulation* 1974; **50:** 436–46.
13 Tajik AJ, Giuliani ER. Echocardiographic observations in idiopathic hypertrophic subaortic stenosis. *Mayo Clin Proc* 1974; **49:** 89–97.
14 Rossen RM, Goodman DJ, Ingham RE, Popp RL. Ventricular systolic septal thickening and excursion in idiopathic hypertrophic subaortic stenosis. *N Engl J Med* 1974; **291:** 1317–9.
15 Cohen MV, Cooperman LB, Rosenblum R. Regional myocardial function in idiopathic hypertrophic subaortic stenosis; an echocardiographic study. *Circulation* 1975; **52:** 842–7.

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Major venous thrombosis: a complication of transvenous pacemaker electrodes

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SUMMARY Two patients with transvenous permanent pacemakers developed thrombosis and occlusion of the superior vena cava around a broken pacing wire, with clot extending into the innominate, subclavian, and axillary veins. Both patients had symptoms and signs of the superior vena cava syndrome which failed to resolve despite anticoagulant and thrombolytic treatment. Obstruction to venous flow, however, was relieved in large measure by the development of collateral venous channels. One of the patients has shown mild symptoms for two years and the other for two months of follow-up. It is suggested that anticoagulant prophylaxis should be given to all patients with a broken wire which cannot easily be removed.

Common complications of permanent transvenous pacing include displacement of electrodes from the original contact points, infection at the site of the generator and of the wire track, cardiac perforation, an increase of pacing threshold caused by fibrosis around the electrode tip, and intravascular migration of severed electrodes.[1] Major venous thrombosis resulting from endocardial pacing electrodes occurs rarely. The two patients reported here developed a chronic superior vena cava syndrome secondary to progressive thrombosis around the broken transvenous pacemaker electrode. Both had two pacing wires within the cardiovascular system: the new wire and the one that had been implanted previously which was broken and remained firmly attached to the right ventricle with the proximal end lying free in the superior vena cava. The patients showed neither resolution of the thrombus nor recanalisation of the involved vessels after anticoagulant and fibrinolytic treatment. Restoration of adequate venous flow occurred spontaneously with the development of collateral venous channels.

Case reports

CASE 1

A 54-year-old woman was admitted to the hospital in February 1977 with two months' history of swelling of the face, chest, and arms. The patient had a transvenous pacemaker implanted in December 1974 for sick sinus syndrome. Two weeks later she underwent an operation because of loss of stimulation. At operation the pacing wire (LEM 603) was found to be damaged near the connection to the pulse generator. An attempt was made to remove the wire, but the distal 24 cm remained in the right ventricle, right atrium, and superior vena cava. A new pacemaker wire was inserted into the right ventricle through the right external jugular vein. The postoperative course was uneventful and the patient was discharged with a normally functioning pacemaker.

When the patient was readmitted she was complaining of headache and dyspnoea on effort. There was oedema and cyanosis of the face, neck, right arm, and upper part of the chest. The external jugular veins were distended, and venous engorgement was present in the upper arm and the pectoral region. The blood pressure was 140/80 mmHg, and the pulse rate 72/min and regular. The chest *x*-ray film confirmed the presence of the pacing wire and the broken wire. Blood chemistry was normal except for a prolonged euglobulin lysis time to 320 min (normal 231 ±66 min). A clinical diagnosis of occlusion of the superior vena cava was made and heparin (5000 units) was administered intravenously every four hours. There was no improvement within one week of anticoagulation. Venography showed thrombosis in the right and proximal portion of the left innominate vein and the superior portion of the superior vena cava, and there was evidence of collateral circulation through the superficial and deep veins of the neck to the

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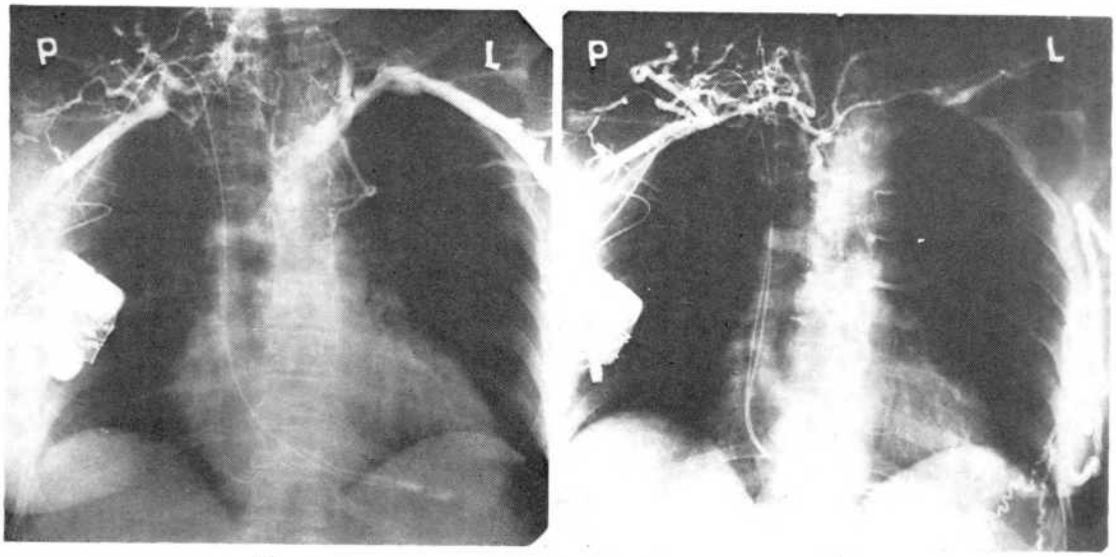
azygos vein (Fig. 1a). The patient was placed on a regimen of streptokinase—a starting dose of 250 000 units intravenously followed by a maintenance dose of 100 000 units/hour over the next 92 hours in a continuous infusion. This produced a satisfactory fibrinolytic state: lysis time was shortened to 10 to 20 minutes. Long-term anticoagulant treatment with heparin was started simultaneously. The drug was subsequently changed to dicoumarol and the treatment was continued. Within 48 hours after streptokinase had been started oedema of the face and neck diminished moderately, but swelling of the right arm remained. Venography was not performed.

In May 1977 she underwent a successful replacement of the pacemaker generator. In December 1977 she was admitted to the hospital for re-evaluation. Physical examination showed only slight swelling of the face and arms. Venography showed progressive thrombosis in the superior vena cava extending into both innominate and subclavian veins and the left axillary vein, as compared with the former examination (Fig. 1b). The development of collateral venous channels was also seen. The patient was treated with urokinase, an intravenous loading dose of 7200 CTA units/kg body weight over 10 minutes, followed by a maintenance dose of 3600 CTA units/kg per hour over six hours in a continuous infusion. The treatment was then continued with streptokinase 100 000 units/hour over 72 hours, followed by heparin and long-term anticoagulation with dicoumarol and dipyridamole. Recanalisation of major veins was not achieved. The patient has shown mild symptoms for two years of follow-up and has required diuretics twice a week.

CASE 2

This 72-year-old man was admitted to hospital in November 1978 because of swelling of the face and arms for 10 days. He had a transvenous pacemaker implanted three years before admission for complete heart block. Eleven months before admission there was loss of stimulation because of an increase in the pacing threshold. An attempt was made to remove the electrode which resulted in breakage of the wire. The broken wire remained attached to the right ventricle with the proximal end lying free in the superior vena cava. A new electrode was placed into the right ventricular apex through the right jugular vein. The patient was discharged with a normally functioning pacemaker. On the present admission he complained of headache and dyspnoea on exertion. His face was oedematous and cyanotic, the external jugular veins were distended, and the arms were swollen. Blood pressure was 130/70



a

b

Fig. 1 *Case 1.* (a) *Superior venacavogram taken before treatment showing complete occlusion of the superior vena cava up to the junction of the azygos vein as well as of the right innominate, subclavian, and proximal portion of the left innominate vein. Collateral circulation from the neck veins to the azygos system.* (b) *Ten months later, occlusion extended into the innominate system, both the subclavians, and the left axillary vein. Venous collateral circulation increased.*

mmHg, and the pulse rate 72/min and regular. Electrocardiogram showed a normally functioning pacemaker. Chest x-ray film showed slight cardiac enlargement and the presence of the working electrode as well as the broken wire. Venography showed complete occlusion of the superior vena cava, innominate system, and proximal portion of the subclavian veins, with multiple collateral veins in the axilla, chest wall, and neck (Fig. 2). The patient was treated with heparin for two days followed by streptokinase in an initial dose of 250 000 units and a maintenance dose of 100 000 units/hour over 96 hours in a continuous intravenous infusion. During this time oedema of the face and arms decreased. Venography performed three weeks after fibrinolytic treatment showed no recanalisation of the vessels. Collateral circulation was well developed. Long-term anticoagulant treatment has been continued, and the patient has shown mild symptoms for two months of follow-up and has required diuretics once a week.

Discussion

Thromboembolism is a rare but potentially life-threatening complication of transvenous cardiac pacemakers. So far only a few cases have been reported, with thrombosis of the axillary, subclavian, and innominate veins or of the superior vena cava,[2-4] and fatal pulmonary embolism resulting from thrombosis in the right heart and major veins.[5-7] Crook *et al.*[8] reviewed a series of 125 patients on permanent transvenous pacing and found occlusion of the subclavian vein in only three of these patients. Subclinical thrombosis, however, may occur frequently as a result of pacemaker insertion. A venographic study by Balau *et al.*[9] in 49 patients, after pacemaker insertion through the cephalic vein, showed radiological evidence of thrombi in 14, but only three of them developed oedema of the arm. A recently reported venography study[10] in 34 patients showed partial or total obstruction of the innominate or subclavian veins in 22. Collateral circulation was well developed in most of them. The superior vena cava syndrome secondary to thrombosis along the course of the pacing wire may be encountered immediately or as late as 15 months after pacemaker insertion. Most of these patients respond well to heparin or to streptokinase treatment, particularly when recognised early.[3 4 11]

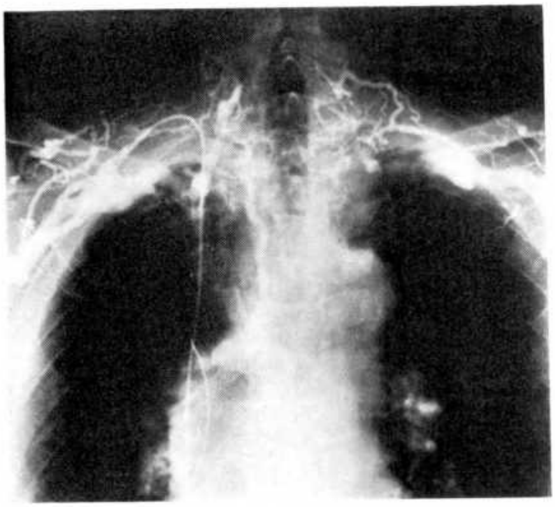


Fig. 2 *Case 2. Total occlusion of the superior vena cava, innominate system, and the proximal portion of subclavian veins, with collateral circulation through the neck and chest wall veins. Note the presence of the broken pacemaker wire in the superior vena cava.*

Our two patients developed symptomatic major venous thrombosis around the broken electrode wire as late as 11 months and three years after pacemaker insertion, respectively. In both instances the remnant of the electrode which we failed to remove served as a continuous trigger for thrombus formation. Damage to the endothelium of the superior vena cava caused by persistent movement of the broken wire firmly attached to the beating heart could have been the major predisposing factor.

Initially, case 1 had thrombotic occlusion of the superior vena cava as well as the right and a short proximal portion of the left innominate vein. Clinical onset, however, was silent and the superior vena cava syndrome developed gradually over two months. Streptokinase treatment instituted at the time of advanced organisation failed to resolve the thrombi. Despite long-term anticoagulant prophylaxis thrombosis was progressive. Venography at 10 months of follow-up revealed extension of the thrombosis into both innominate and subclavian veins and the left axillary vein. Because of active thrombosis another course of fibrinolytic treatment with urokinase followed by streptokinase was administered but recanalisation of the vessels was not achieved. Fibrinolytic treatment was also not effective in the second patient who had shown signs and symptoms of the superior vena cava syndrome for two weeks before streptokinase was started. Obstruction to venous flow, however, was relieved in great part in both patients by the development of collateral circulation.

As experience with fibrinolytic treatment in venous thrombosis has been accumulated it has become clear that this treatment effectively lyses clots of recent origin. Occasionally even clots of more than 10 days' existence may be lysed, but the success of treatment is, in general, inversely proportional to the age of the clot.[12] Successful streptokinase treatment, however, was reported in chronic arterial occlusive disease, provided organisation of thrombi is greatly delayed.[13] Though treatment with streptokinase carries a risk of excessive bleeding and is generally unsuccessful in long-lasting thrombosis, we applied this form of treatment because of clinical suspicion that the thrombosis was still active, and in the hope of reducing the extension of venous occlusion.

Review of our two cases clearly indicates that there is a definite risk of major venous thrombosis after pacemaker insertion if a broken pacing wire is retained in the cardiovascular system. We believe that all patients with a broken wire, which cannot easily be removed, should be on long-term anticoagulant therapy.

References

1 Chardack WM. Cardiac pacemakers and heart block. In: Gibbon JH Jr, Sabiston DC Jr, Spencer F, eds. *Surgery of the chest.* Philadelphia: WB Saunders, 1969: 824.

2 Griepp RB, Daily PO, Shumway NE. Subclavian-axillary vein thrombosis following inplantation of a pacemaker catheter in the internal jugular vein. *J Thorac Cardiovasc Surg* 1970; **60:** 889–92.

3 Friedman SA, Berger N, Cerutti MM, Kosmoski J. Venous thrombosis and permanent cardiac pacing. *Am Heart J* 1973; **85:** 531–3.

4 Williams DR, Demos NJ. Thrombosis of superior vena cava caused by pacemaker wire and managed with stroptokinase. *J Thorac Cardiovasc Surg* 1974; **68:** 134–7.

5 Prozan GB, Shipley RE, Madding GF, Kennedy PA. Pulmonary embolism in the presence of an endocardiac pacing catheter. *JAMA* 1968; **206:** 1564–5.

6 Reynolds J, Auslinger D, Yore R, Paine R. Transvenous cardiac pacemeker, mural thrombosis and pulmonary embolism. *Am Heart J* 1969; **78:** 688–91.

7 Kaulbach MG, Krukonis EE. Pacemaker electrode-induced thrombosis in the superior vena cava with pulmonary embolization. A complication of pervenous pacing. *Am J Cardiol* 1970; **26:** 205–7.

8 Crook BRM, Gishen P, Robinson CG, Oram S. Occlusion of the subclavian vein associated with cephalic vein pacemaker electrodes. *Br J Surg* 1977; **64:** 329–31.

9 Balau J, Buysch KH, Marx E, Seling A, Knierem HJ. Thrombose der Vena subclavia nach transvenoser Schrittmacherimplantation. *Radiologie* 1971; **11:** 50–3.

10 Horwitz N. Venous obstruction seen to follow pacing. *Med Tribune* 1976; **32:** 17–21.

11 Sethi GK, Bhayana JN, Scott SM. Innominate venous thrombosis: a rare complication of transvenous pacemaker electrodes. *Am Heart J* 1974; **87:** 770–2.

12 Ockene IS, Dalen JE. The role of fibrinolytic agents in the treatment of thromboembolism. In: Donoso E, Haft J, eds. *Current cardiovascular topics. Thrombosis, platelets, anticoagulation and acetylsalicic acid. Vol 2.* Stuttgart: Georg Thieme, 1976: 44–59.

13 Martin M, Schoop W, Zietler E. Streptokinase in chronic arterial occlusive disease. *JAMA* 1970; **211:** 1169–73.

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Conduction defects and mitral annulus calcification

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SUMMARY The incidence of conduction defects in patients with mitral annular calcification was studied in 104 patients and 121 matched controls. The patients comprised 49 men and 55 women, whose ages ranged from 42 to 90 years, with a mean of 70±9 (±SD). The control group consisted of 121 patients without mitral annular calcification, whose ages ranged from 50 to 90 years, with a mean of 68±8 (±SD); there were 61 men and 60 women. Atrial fibrillation with a slow ventricular response, atrioventricular, or fascicular block were found in 73 patients (70%) with mitral annular calcification (37 men and 36 women) compared with 41 patients (34%) in the control group (24 men and 17 women). Of the 53 patients with isolated calcification of the posterior mitral annulus, 36 (68%) had conduction defects. Both anterior and posterior mitral annular calcification were present in 43 patients, and 29 (67%) of these had conduction defects. Sixty-eight patients had both mitral annular calcification and aortic calcification and 49 (72%) had conduction defects. In the control group, 20 patients had aortic calcification and only seven (35%) had conduction defects. Thus, a significantly increased incidence of conduction defects is present in patients with mitral annular calcification when compared with controls, and this is uninfluenced by sex. The incidence of conduction defects with posterior mitral annular calcification is similar to that found with combined anterior and posterior mitral annular calcification. Aortic calcification, either alone or with mitral annular calcification, is not associated with an increase in the incidence of conduction defects.

Calcification of the mitral valve annulus is generally considered a degenerative process. Various pathological and clinical studies[1-6] have noted a high incidence of such calcification in the elderly and its frequent association with murmurs, cardiac failure, and conduction defects, and have emphasised the striking distortion of the anatomy of the left ventricle, left atrium, and mitral valve apparatus by massive mitral annular calcification. Its clinical detection in the past was based upon the presence of a C- or J-shaped density within the cardiac silhouette on chest *x*-ray films or at fluoroscopy, but recently echocardiography has been shown to be the more sensitive tool.[7] With the widespread use of echocardiography, therefore, more patients with mitral annular calcification are being detected, and this apparent increase in the incidence may be attributed to the diagnostic sensitivity of the investigation as well as to the number of echocardiograms now being performed. Though the association of mitral annular calcification and cardiac conduction defects is recognised,[1 8-11] the true incidence of the latter remains uncertain and the purpose of this study was to determine it. Since mitral annular calcification occurs predominantly in the elderly, who are more likely to have cardiac disorders and conduction defects, we also studied a control group.

Subjects and methods

Consecutive echocardiograms performed at our institution from 1974 to 1978 were reviewed. One hundred and four patients with mitral annular calcification were found (group 1); 121 patients without mitral annular calcification, who were similar to group 1 patients with regard to age and sex distribution, were selected as controls (group 2). The outpatient and hospital records of these patients provided the clinical data, and the incidence of cardiac conduction defects was obtained from an analysis of all the available surface electrocardiograms, undertaken independently without knowledge of the echocardiographic findings.

Echocardiograms were obtained with a com-

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mercially available ultrasonograph using a 1·27 cm, 2·25 MHz, medium-focused transducer, and a strip chart recorder. Posterior mitral annular calcification was identified when a dense echo, greater than 3 mm in width, was shown anterior to the left ventricular posterior wall, and moving parallel with it (Fig.). In addition, the longitudinal sweep of the transducer showed cephalad termination of the echoes at the atrioventricular junction. When the transducer was directed caudally, the echoes from the mitral annular calcification faded into the echoes of the posterior left ventricular wall. Anterior mitral annular calcification was identified when the scans from the left ventricle to the aortic root disclosed a continuous band of echoes at the level or plane of the anterior mitral valve leaflet, both in systole and diastole. The anterior mitral annular calcification and the mitral valve leaflet were in continuity with the posterior wall of the aortic root.

Aortic calcification was recognised when thick bands of echoes were seen within the aortic root walls both in systole and diastole. The presence of echoes consistent with aortic calcification, however, was not necessarily associated with aortic valvular calcification or with a reduction in the maximal systolic opening of the aortic valve leaflets.

In the electrocardiograms atrioventricular and fascicular blocks were diagnosed using standard criteria.[12 13] An intraventricular conduction defect was diagnosed in the presence of a QRS duration equal to or greater than 120 ms but not meeting the criteria for complete right or left bundle-branch block. Atrial fibrillation and/or flutter with a slow ventricular response (defined as less than 60 beats/minute) was considered significant only if drugs were not being given.

Statistical analysis was performed using χ^2 and Student's t test whenever appropriate.

Results

The clinical data of the 104 patients in group 1 and the 121 patients in group 2 are summarised in Table 1. The age range was 42 to 90 years, with a mean of 70 (SD = 9) in group 1 and 50 to 90 years, with a mean of 68 (SD = 8) in group 2. There were 49 men and 55 women in group 1 and 61 men and 60 women in group 2. Echocardiography was performed for a cardiac murmur in 66 patients in group 1 and 58 patients in group 2, and to evaluate left ventricular function in 29 patients from group 1 and 54 from group 2. Nine patients in each group underwent echocardiography for miscellaneous reasons, such as pericardial effusion, atypical chest pain, and the detection of a possible source of systemic emboli.

A systolic ejection murmur along the left sternal border or at the second right intercostal space suggesting left ventricular outflow tract obstruction or an aortic valve origin was present in 67 patients in group 1 and 54 patients in group 2. A holosystolic murmur heard best at the apex and consistent with mitral regurgitation was present in 17 patients in group 1 and 21 patients in group 2. Ten patients in group 1 and 11 patients in group 2 had an early diastolic decrescendo murmur along the left sternal border consistent with aortic regurgitation. A mid-diastolic murmur at the apex with or without presystolic accentuation suggestive of mitral stenosis was present in seven patients in group 1 and four patients in group 2; in none of these patients, however, was there the anterior motion of the posterior leaflet of the mitral valve characteristic of rheumatic mitral stenosis. Eleven patients in group 1 and nine patients in group 2 had a combination of two or more murmurs.

Twenty-six patients in group 1 and 37 in group 2 had hypertension. Diabetes mellitus was present in

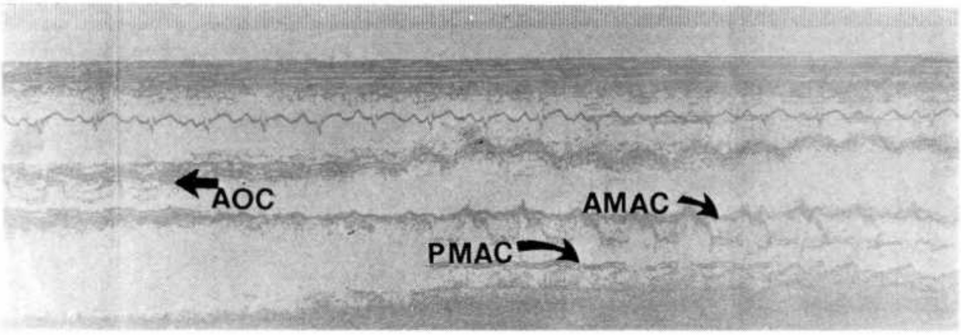

Fig. *Echocardiogram. AOC, aortic wall calcification; PMAC, posterior mitral annular calcification; AMAC, anterior mitral annular calcification.*

Table 1 *Clinical findings*

	Age (y) *($\bar{x}$ ±SD)*	*Sex*		*Total*	*Associated conditions*				*Murmurs*				*Cardiomegaly*	
		Men	*Women*		*AODM*	*Hypn*	*CHD*	*RHD*	*AS*	*AR*	*MS*	*MR*	*X-ray*	*Echo*
<70	Group 1 (62 ±7)	22	19	41	5	10	11	1	23	2	3	9	35	31
	Group 2 (62 ±6)	35	28	63	6	23	28	5	25	5	2	13	33	35
⩾70	Group 1 (76 ±6)	27	36	63	7	16	19	2	44	8	4	8	42	44
	Group 2 (75 ±4)	26	32	58	6	14	20	2	29	6	2	8	32	28
Total	Group 1 (70 ±9)	49	55	104	12	26	30	3	67	10	7	17	77	75
	Group 2 (68 ±8)	61	60	121	12	37	48	7	54	11	4	21	65	63

$\bar{x}$, mean age; AODM, adult onset diabetes mellitus; AR, aortic regurgitation; AS, aortic stenosis; CHD, coronary heart disease; Echo, echocardiogram; Hypn, hypertension; MR, mitral regurgitation; MS, mitral stenosis; RHD, rheumatic heart disease; SD, standard deviation.

12 patients in each group. Thirty patients in group 1 and 48 in group 2 had coronary heart disease. A history of rheumatic fever was present in only three patients of group 1 and seven of group 2 (Table 2).

Cardiomegaly detected by a cardiothoracic ratio on chest *x*-ray greater than 50 per cent was present in 77 patients in group 1 and 65 in group 2. Echocardiography showed that 48 patients in group 1 and 46 patients in group 2 had left atrial enlargement, 53 patients in group 1 and 49 in group 2 had left ventricular enlargement, 26 patients in group 1 and 30 in group 2 having both.

Table 2 *Correlation of associated conditions and conduction defects*

Associated conditions	*Patients with MAC (104)*		*Patients without MAC (121)*	
	CD(73)	*NCD(31)*	*CD(41)*	*NCD(80)*
Hypertension	18 (24%)	8 (26%)	13 (32%)	24 (30%)
Diabetes	9 (12%)	3 (10%)	4 (10%)	8 (10%)
CHD	23 (31%)	7 (23%)	13 (32%)	35 (43%)
RHD	2 (3%)	1 (3%)	2 (5%)	5 (6%)
Total	52 (70%)	19 (62%)	32 (79%)	72 (89%)

CHD, coronary heart disease; CD, conduction defect; MAC, mitral annular calcification; NCD, no conduction defect; RHD, rheumatic heart disease.

The types of conduction defects identified in groups 1 and 2 are summarised in Tables 3 and 4. Seventy-three of the 104 patients in group 1 had them, an incidence of 70 per cent (37 men and 36 women). There were 53 patients with isolated calcification of the posterior mitral annulus. Thirty-

Table 3 *Correlation of conduction defects with age and sex*

Sex	*Age (y)*	*AF c̄ SVR*		*1° AVB*		*2° AVB M1**		*3° AVB*		*RBBB*		*LBBB*		*LAHB*		*IVCD*		*Total patients*		*Patients with CD*	
		1	*2*	*1*	*2*	*1*	*2*	*1*	*2*	*1*	*2*	*1*	*2*	*1*	*2*	*1*	*2*	*1*	*2*	*1*	*2†*
Men	<70	9	5	1	5	0	0	2	1	0	0	2	4	3	3	3	1	22	35	16	14
	⩾70	8	5	4	2	1	0	2	0	1	0	6	2	7	2	2	1	27	26	21	10
Women	<70	9	1	1	2	0	0	1	0	2	0	2	0	2	2	1	0	19	28	13	5
	⩾70	11	6	7	1	0	0	3	0	2	1	9	1	6	2	0	1	36	32	23	12
Total		37	17	13	10	1	0	8	1	5	1	19	7	18	9	6	3	104	121	73	41

AF c̄ SVR, atrial fibrillation with slow ventricular response; AVB, atrioventricular block; CD, conduction defect; IVCD, intraventricular conduction defect; LAHB, left anterior hemiblock; LBBB, left bundle-branch block; M1, Mobitz 1; RBBB, right bundle-branch block; 1, patients with mitral annular calcification; 2, patients without mitral annular calcification.

* None of the patients had Mobitz 2, 2° AVB in either group. † Some patients with more than one conduction defect.

Table 4 *Correlation of conduction defects with type of calcification*

Type of calcification	*No. of patients*	*Patients with CD*	*AF $\bar{c}$ SVR*	*1° AVB*	*2° AVB M1**	*3° AVB*	*RBBB*	*LBBB*	*LAHB*	*IVCD*	*Combined*
Ant MAC	8	8	1	4	0	1	0	3	2	1	3
Post MAC	53	36	18	6	1	5	0	10	6	4	14
Ant and post MAC	43	29	18	3	0	2	5	6	10	1	12
Total	104	73	37	13	1	8	5	19	18	6	29
MAC and AOC	68	49	19	11	1	4	4	16	12	4	20
AOC only (group 2)	20	7	4	1	0	0	1	2	3	0	3

AF $\bar{c}$ SVR, atrial fibrillation with slow ventricular response; Ant, anterior; AOC, aortic calcification; AVB, atrioventricular block; CD, conduction defect; IVCD, intraventricular conduction defect; LAHB, left anterior hemiblock; LBBB, left bundle-branch block; MAC, mitral annular calcification; M1, Mobitz 1; Post, posterior; RBBB, right bundle-branch block.

* None of the patients had Mobitz 2, 2° AVB in either group.

six of these (68%) had conduction defects (Table 4). Both anterior and posterior mitral annular calcification was present in 43 patients, and 29 (67%) of these had conduction defects. Isolated anterior mitral annular calcification was present in only eight patients. All of these were found to have conduction defects. Sixty-eight of the group 1 patients also had aortic calcification, and 49 (72%) of these had conduction defects.

Of the 121 patients in group 2, only 41 (24 men and 17 women) had conduction defects, an incidence of 34 per cent compared with 70 per cent in group 1. Aortic calcification in the absence of mitral annular calcification was present in 20 patients in group 2. Seven of these (35%) had conduction defects, an incidence similar to that of the group in general.

There were 41 patients in group 1 who were under the age of 70 (Table 1). Of these, 16 of the 22 men (73%) and 13 of the 19 women (68%) had conduction defects, an overall incidence of 71 per cent. Of the 63 patients in group 1 over the age of 70 years, 21 of the 27 men (78%) and 27 of the 36 women (75%) were found to have conduction defects, an overall incidence of 76 per cent. In group 2, 63 patients were under 70 years of age. Of these, 14 of the 35 men (40%) and five of the 28 women (18%) had conduction defects, an overall incidence of 30 per cent. Of the 58 patients in group 2 over the age of 70, 10 of the 26 men (38%) and 12 of the 32 women (38%) had conduction defects, an overall incidence of 38 per cent. Thus, in group 1 age and sex appeared to have no influence on the occurrence of conduction defects.

Discussion

Bönninger[1] first described mitral annular calcification as a pathological entity and pointed out its association with heart block. Since then, several reports describing the pathological and clinical features of mitral annular calcification have appeared.[2–5] Pathological studies have shown that the deposits of calcium occur predominantly in the posterior portion of the annulus but may extend into the left atrium and left ventricle behind the mitral valve leaflets.[4, 5] The deposits of calcium may be extensive, 1 to 3 cm in diameter, and may encircle all or most of the mitral orifice. The calcium may extend as far as 3 to 4 cm into the adjacent myocardium. Calcific deposits may also extend into the membranous portion of the intraventricular septum in the vicinity of the bundle of His and its branches. Unlike secondary calcification in rheumatic heart disease, direct involvement of the mitral leaflets by these calcific deposits is infrequent. There have, however, been several cases of mitral annular calcification reported with commissural adherence of the mitral valve leaflets and calcific deposits in the anterior leaflet of the mitral valve as well as restriction of the motion of the posterior leaflets.[14] Calcification of the aortic root has been a frequently associated finding in patients with mitral annular calcification, with an incidence as high as 74 per cent in one series.[14] This is similar to the incidence of 65 per cent noted in our own study. The murmur of mitral regurgitation has frequently been noted in patients with mitral annular calcification, and the mitral regurgitation is felt to be the result of interference with the normal function of the mitral valve apparatus, either because of the lack of normal sphincter action of the annulus as a result of pronounced calcification or because of distortion of the mitral valve leaflets caused by heavy deposits of calcium in them.[3, 14] More recently, mitral valve obstruction with haemodynamically documented diastolic gradients across the mitral valve during diastole have been reported in four patients with massive mitral annular calcification.[15] Though not proven, the mitral annular calcification may have been the source of many of the murmurs heard in our patients. However, the frequency of cardiac murmurs of all types, both systolic and diastolic, was similar in the patients without mitral annular calcification.

Clinically, three methods are available for the detection of mitral annular calcification. Firstly, the chest *x*-ray, which, in our experience, was poorly sensitive, 30/104 (31%). Secondly, there is image intensification fluoroscopy. This has been shown to have high sensitivity in diagnosing cardiac calcification.[16 17] Cardiac fluoroscopy and/or cineangiograms were available in 22 patients in group 1, and in all mitral annular calcification was detected. Lastly, many recent reports have described the usefulness of echocardiography.[18–25]

The incidence of mitral annular calcification has been reported to be 8 to 10 per cent in necropsied series over the age of 50 years and this incidence increases in a linear fashion with advancing age.[4] Though the majority of reported series of mitral annular calcification have shown a much higher incidence in women, as high as 3 or 4 to 1, our study disclosed an equal sex incidence. This is in agreement with the series of 87 cases reported by Perloff and Roberts[14] in which a similar sex distribution was also found.

Several studies[2 9 26] have reported an increased incidence of mitral annular calcification in patients with diabetes mellitus and hypertension. Our study did not confirm this, nor was the incidence of coronary heart disease different in patients compared with controls.

A number of previous reports had noted cardiac conduction defects associated with a calcified mitral annulus,[1 8 10 11 27] but the true incidence of them was uncertain. Our study showed cardiac conduction defects in 70 per cent of 104 patients, a figure significantly greater than in the control group.

Conduction defects are so common with mitral annular calcification probably because of the close association of the atrioventricular node and bundle of His to the cardiac fibrous skeleton.[28] Others have suggested that the degenerative process within the mitral annulus may be associated with or accompanied by a "sclerodegenerative process" within the conduction system in these elderly patients.[29 30] Though the exact mechanism underlying atrial fibrillation is not certain, it has been suggested that the diffuse conduction system disease may interrupt inter- and intra-atrial conduction.[31] We postulate that involvement of the atrioventricular node and/or His bundle by annular calcification may be responsible for the presence of the slow ventricular response in these patients.

The incidence of conduction defects associated with calcification restricted to the posterior portion of the mitral annulus was similar to that found in patients having both anterior and posterior mitral annular calcification. Further, the presence of additional aortic calcification was not associated with a statistically significant increase in this incidence. Isolated aortic calcification in the absence of mitral annular calcification was found in 20 patients in group 2. The incidence of conduction defects in these patients was not significantly different from that found in the remainder of the group who did not have aortic calcification (35% versus 34%). All eight patients with anterior mitral annular calcification had conduction defects but the significance of this finding is uncertain because the number is small.

Clinical implications

Our study confirms the increased incidence of conduction defects in patients with mitral annular calcification, irrespective of age, sex, or associated conditions. Long-term follow-up studies are needed to determine how such conduction defects develop and progress. Patients with mitral annular calcification who do not have conduction defects in the surface electrocardiogram probably need closer observation and should be considered for ambulatory monitoring and/or electrophysiological investigation of the conduction system, especially if they have symptoms.

References

1. Bönninger M. Zwei Falle von Herzblock. *Dtsch Med Wochenschr* 1908; **34:** 2292.
2. Fertman MH, Wolff L. Calcification of mitral valve. *Am Heart J* 1946; **31:** 580–9.
3. Liu SF, Simon MA. Calcification of the mitral valve annulus and its relation to functional valvular disturbance. *Am Heart J* 1954; **48:** 497–505.
4. Korn D, DeSanctis RW, Sell S. Massive calcification of the mitral annulus: a clinicopathological study of fourteen cases. *N Engl J Med* 1962; **267:** 900–9.
5. Pomerance A. Pathological and clinical study of calcification of the mitral ring. *J Clin Pathol* 1970; **23:** 354–61.
6. Schott CR, Kotler MN, Parry WR, Segal BL. Mitral annular calcification. *Arch Intern Med* 1977; **137:** 1143–50.
7. Gabor GE, Mohr BD, Goel PC, Cohen B. Echocardiographic and clinical spectrum of mitral annular calcification. *Am J Cardiol* 1976; **38:** 836–42.
8. Gibson GA, Richie WT. Historic instances of Adams-Stokes syndrome due to heart-block. *Edinb Med J* 1909; **2:** 507–25.
9. Geerling JC. Calcification in annular sclerosis of heart valves in arteriosclerosis. *Ned Tijdschr Geneeskd* 1929; **2:** 5633.
10. Yater WM, Cornell VH. Heart block due to calcareous lesions of the bundle of His. *Ann Intern Med* 1935; **8:** 777–89.
11. Comeau WJ. Paroxysmal complete heart block

alternating with normal sinus rhythm and conduction. *Am J Med Sci* 1937; **194:** 43–53.

12 Johnson RL, Averill KH, Lamb LE. Electrocardiographic findings in 67 375 asymptomatic subjects. VII. Atrioventricular block. *Am J Cardiol* 1960; **6:** 153–77.

13 Rosenbaum MB, Elizari MV, Lazzari JO. *The hemiblocks.* Oldsmar, Florida: Tampa Tracings 1970.

14 Perloff JK, Roberts WC. Mitral valvular disease: a clinicopathologic survey of the conditions causing the mitral valve to function abnormally. *Ann Intern Med* 1972; **77:** 939–75.

15 Hammer WJ, Roberts WC, deLeon KC Jr. "Mitral stenosis" secondary to combined "massive" mitral annular calcific deposits and small, hypertrophied left ventricles. *Am J Med* 1978; **64:** 371–6.

16 McCarthy JH, Palmer FJ. Incidence and significance of coronary artery calcification. *Br Heart J* 1974; **36:** 499–506.

17 Bartel AG, Chen JT, Peter RH, Behar VS, Kong Y, Lester RG. The significance of coronary calcification detected by fluoroscopy. A report of 360 patients. *Circulation* 1974; **49:** 1247–53.

18 Okimato R, Iwasaki T, Mamata C, *et al.* Echocardiographic and phonocardiographic studies of mitral ring calcification. *Cardiovasc Sound Bull (Tokyo)* 1975; **5:** 707.

19 D'Cruz IA, Cohen HC, Prabhu R, Bisla V, Glick G. Clinical manifestations of mitral annulus calcification with emphasis on its echocardiographic features. *Am Heart J* 1977; **94:** 367–77.

20 Ewy G, Groves BM, Shy N, George W, Yauger H. Echocardiographic appearance of mitral annular calcification (abstract). *Circulation* 1975; **51 & 52,** suppl II: 179.

21 Graber HL, Fulkerson PK, Auseon JC. Echocardiographic demonstration of mitral annular calcification (abstract). *Circulation* 1975; **51 & 52,** suppl II: 191.

22 Dashkoff N, Karacushansky M, Fortuin NJ. Echocardiographic features of mitral annulus calcification (abstract). *Circulation* 1975; **51 & 52,** suppl II: 34.

23 Hirschfield DS, Emilson BB. Echocardiogram in calcified mitral annulus. *Am J Cardiol* 1975; **36:** 354–6.

24 Dashoff N, Karacushansky M, Come PC, Fortuin NJ. Echocardiographic features of mitral annulus calcification. *Am Heart J* 1977; **94:** 585–92.

25 Tanabe J, Ibrahim F. Echocardiographic findings of mitral anulus calcification. Special emphasis on clinical usefulness. In: Diethrich EB, ed. *Noninvasive cardiovascular diagnosis.* Baltimore: University Park Press, 1978: 383–92.

26 Tajik AJ, Giuliani ER, Frye RL, Davis GD, McGoon DC, Brandenburg RO. Mitral valve and/or annulus calcification associated with idiopathic subaortic stenosis (abstract). *Circulation* 1972; **45 & 46,** suppl II: 228.

27 Rytand DA, Lipstich LS. Clinical aspects of calcification of the mitral annulus fibrosus. *Arch Intern Med* 1946; **78:** 544–64.

28 Lev M. Anatomic basis for atrioventricular block. *Am J Med* 1974; **37:** 742–8.

29 Lenègre J. Etiology and pathology of bilateral bundle branch block in relation to complete heart block. *Prog Cardiovasc Dis* 1964; **6:** 409–44.

30 Scarpa WJ. The sick sinus syndrome. *Am Heart J* 1976; **92:** 648–60.

31 Fulkerson PK, Beaver BM, Auseon JC, Graber HL. Calcification of the mitral annulus. Etiology, clinical associations, complications and therapy. *Am J Med* 1979; **66:** 967–77.

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Autonomic effects on the human cardiac conduction system*

Evaluation by intracardiac electrocardiography and programmed stimulation techniques

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SUMMARY After right heart catheterisation in 20 subjects, aged 30 to 82 years, the techniques of intracardiac electrocardiography and programmed stimulation were used to determine variables of normal function of the sinuatrial node, atrioventricular node, and intraventricular conduction system. Specific attention was paid to autonomic influences on these variables. These were assessed by comparison of determinations made before and after cardiac autonomic block induced by intravenous atropine, 0·03 mg/kg, and propranolol, 0·15 mg/kg.

Sympathetic and larger depressant vagal effects on sinuatrial node function (sinus cycle length and sinus node recovery time after overdrive atrial pacing) were demonstrated. Autonomic effects on atrioventricular node conduction (AH interval and Wenckebach threshold to incremental right atrial pacing) were small, of similar magnitude (approximately 20% change), and opposing. Only significant vagal effects in increasing the effective and functional refractory periods of the atrioventricular node (pacing at 100 bpm) were demonstrated (approximately 15 and 12% change, respectively). The atrial effective refractory period, duration of the His bundle electrogram, and the HV interval were unchanged by either drug. Effects on refractory periods of the intraventricular conduction system could not be assessed because exact determinations were limited by refractoriness of the atrioventricular node. The QT interval with pacing at 100 bpm decreased significantly after atropine but was unchanged after propranolol.

The techniques of intracardiac electrocardiography[1] and programmed intracardiac stimulation[2 3] have greatly increased the understanding of normal cardiac conduction. This has facilitated recognition of functional disorders of the sinuatrial node,[4] atrioventricular node, and specialised intraventricular conduction system.[5]

Sinuatrial node function may be assessed by measurement of the sinus node recovery time after a period of overdrive atrial pacing,[6 7] and the sinuatrial conduction time after single induced atrial depolarisations.[8] The atrioventricular node and intraventricular conduction system may be assessed by measurement of intracardiac conduction times,[1] the response to rapid atrial pacing,[9] and refractory periods using programmed stimulation.[2]

The normal limits of these electrophysiological variables, however, have been imprecisely defined. It might be expected that this may reflect, at least in part, variations caused by temporal changes in autonomic influences on the heart. This proposition was advanced by Jose and Taylor,[10 11] who suggested that pharmacological block of cardiac sympathetic and parasympathetic efferent nerves by propranolol and atropine, respectively, allowed observation of the intrinsic heart rate.

This present study aimed to apply Jose's technique to quantify autonomic influences on normal automaticity of the sinuatrial node, atrioventricular node conduction and refractoriness, conduction in the intraventricular conduction system, and ventricular repolarisation (as assessed by the QT interval). To our knowledge, such systematic assessment by administration of both drugs to a large group of normal patients has not

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been previously undertaken. It is expected that the observation of responses after autonomic blockade might allow the development of more sophisticated criteria for the recognition of abnormal function.

Subjects and methods

SUBJECTS

Twenty subjects (12 men and eight women, aged 30 to 82 years, mean age 62 years) were studied. Clinical features and investigations, including routine and prolonged electrocardiographic monitoring, had categorised the subjects into two groups. The first (six patients) had either regular narrow QRS tachycardias, observations during electrophysiology study suggesting that these were a result of ectopic atrial tachycardia (two), or re-entry involving the atrioventricular node (one), or they presented with palpitation with no documented or inducible tachycardias (three). The second group (14 patients) had dizzy spells but no apparent cardiac abnormality clinically or during electrophysiology study. Patients with manifest sick sinus syndrome or atrioventricular conduction abnormality, with other medical conditions which contraindicated the use of atropine or propranolol, or with angina which might have been induced by rapid atrial pacing, were specifically excluded. In each case, catheterisation was only performed when the electrophysiology study was considered to be clinically indicated. Written informed consent was obtained after full explanation of the procedure. A full matrix of data was not obtained. Results relate to the total group of 20 patients unless stated.

CATHETERISATION TECHNIQUES

Cardioactive drugs were discontinued for at least five elimination half-lives. Patients were fasted on the morning of their study and were not routinely sedated. Rarely, intravenous diazepam 2·5 to 5 mg was given in a bolus injection during the procedure.

Electrode catheters were introduced percutaneously into the femoral veins and advanced under fluoroscopic control to intracardiac sites.

(a) A quadripolar catheter was sited in the high lateral right atrium in the vicinity of the sinuatrial node. The proximal and distal electrode pairs were used for recording of the high right atrial electrogram and for atrial stimulation, respectively.

(b) A tripolar catheter was sited across the tricuspid valve to record the His bundle electrogram.

(c) A bipolar catheter was advanced to a right ventricular site where ventricular pacing could be immediately initiated.

Intracardiac electrograms were obtained by filtering out frequencies below 50 Hz and above 500 Hz. Simultaneous recordings of electrocardiographic leads I, II, and VI, and high right atrial, medial right atrial, His bundle, and right ventricular electrograms were made concurrently on a 0·5 in magnetic tape with play-back facilities (Ampex) and on a six-channel direct writing recorder (Elema Mingograph E 141E/A) at paper speed 100 mm/second.

Intracardiac stimulation was performed using a programmable stimulator (Devices Neurolog) that delivered impulses of 2 ms duration and voltage output approximately twice diastolic threshold The stimulator enabled both fixed rate cardiac. pacing at variable rates and introduction of atrial premature beats after every eight atrial paced beats.

During each of the three periods, before drugs, after atropine or propranolol, and after both drugs (atropine + propranolol or propranolol + atropine), the following measurements were made.

(a) Intracardiac conduction intervals:

(*i*) Basic sinus cycle length (ms);

(*ii*) AH interval (ms) measured from the high-frequency deflection of the medial right atrial electrogram (A) to the onset of His bundle depolarisation (H). This interval is a measure of atrioventricular nodal conduction time; and

(*iii*) HV interval (ms) measured from the onset of H to the earliest onset of ventricular activation from any surface electrocardiographic lead or the right ventricular electrogram (V). This measures conduction time through the His-Purkinje tissue.

(b) The sinus node recovery time measured as the time for recovery of spontaneous sinus node activity after 60 seconds of overdrive high right atrial pacing. Sinus node recovery time was measured between the high-frequency deflections of the relevant high right atrial electrograms, and determined five times at each of two atrial pacing rates, 100 and 130 bpm. Determinations were discarded when a junctional escape beat terminated the post-pacing pause. The pooled means of the five determinations for each patient at each pacing rate were used for statistical analysis of the effects of autonomic blockade.

(c) The response to incremental high right atrial pacing. Pacing was started at a rate just greater than the inherent sinus rate and progressively increased by 10 bpm each 30 seconds until atrioventricular nodal Wenckebach resulted (Wenckebach threshold, in beats per minute).

(d) The refractory periods of the cardiac conducting tissue as measured by the extrastimulus technique.[2] Determinations were made at the same basic rate of atrial pacing, viz. 100 bpm. This elimated variations caused by the cycle length-dependence of cardiac refractoriness.[12]

(*i*) Effective refractory period of the atrium = the longest coupling interval of an extrastimulus (S_1S_2) which failed to induce atrial depolarisation;

(*ii*) Effective refractory period of the atrioventricular node = the longest coupling interval of an induced atrial depolarisation (A_1A_2) which failed to propagate to the bundle of His;

(*iii*) Functional refractory period of the atrioventricular node = the shortest propagated response to the His bundle (H_1H_2) resulting from any coupling interval of the atrial extrastimulus; and

(*iv*) Relative refractory period of the intraventricular conduction system = the longest H_1H_2 coupling interval which resulted in either aberrant intraventricular conduction (identified from the surface electrocardiogram leads), or prolongation of intraventricular conduction of the extrastimulus (H_2V_2).

(e) The QT interval measured from the last beat of one minute right atrial pacing at rates 100 and 130 bpm. This technique eliminated the need for correction of the QT interval for heart rate.[13] The interval was averaged from the five sequences of atrial pacing and measured from the onset of the QRS complex to the time for return of the T wave to the isoelectric line.[14] Though three approximately mutually perpendicular electrocardiographic leads were deliberately recorded, in general lead II was chosen for more precise measurements.

For each of these measurements the limit of accuracy was considered to be 5 ms.

DRUGS

Atropine was administered in an intravenous bolus dose of 0·03 mg/kg then 0·006 mg/kg per 30 min, to produce vagal block. Electrophysiological measurements were started when sinus cycle length had decreased to a stable level, usually after two to three minutes.

Propranolol was used to produce cardiac sympathetic block. The drug was given by intravenous administration of 1 mg/min to a total dose of 0·15 mg/kg. When necessary, a subsequent dose of 0·03 mg/kg was given 30 minutes later. Arterial pressure was monitored at each minute. Electrophysiological measurements were started 15 minutes after administration of the drug.

STATISTICAL METHODS

Determinations for all patients in each treatment period were pooled, and results expressed by mean ± standard error of the mean. Student's t test for related variables was used for statistical analysis, a p value $< 0{\cdot}05$ being regarded as significant.

Results

The electrophysiological data obtained are summarised in the Table.

Table *Summary of electrophysiological variables before and after autonomic block (propranolol plus atropine or atropine plus propranolol)*

Variable	*Resting*	*Autonomic blockade*
Sinus cycle length (ms)	929 ±38	791 ±34
AH interval (ms)	78 ±5	77 ±5
SNRT (RAP 100 bpm) (ms)	1121 ±41	928 ±42
SNRT (RAP 130 bpm) (ms)	1079 ±40	955 ±40
Wenckebach threshold AV node (bpm)	157 ±7	158 ±6
ERP AV node (RAP 100 bpm) (ms)	298 ±19	277 ±14
FRP AV node (RAP 100 bpm) (ms)	408 ±19	389 ±18
QT interval (RAP 100 bpm) (ms)	334 ±3	325 ±5
QT interval (RAP 130 bpm) (ms)	314 ±4	304 ±5

SNRT, sinus node recovery time; ERP, effective refractory period; FRP, functional refractory period; RAP, right atrial pacing.

SINUS CYCLE LENGTH AND INTRACARDIAC CONDUCTION INTERVALS

The effects of cardiac autonomic block on sinus cycle length in all 20 patients are shown in Fig. 1. Vagal effects could be judged by the decrease in cycle length after initial atropine administration (mean decrease 356 ms, $p < 0{\cdot}001$) and after atropine administration in those who had already received propranolol (mean decrease 243 ms, $p < 0{\cdot}001$). Sympathetic effects, as judged by the increase in cycle length after initial propranolol administration (mean 89 ms, $p < 0{\cdot}05$) and after administration to subjects subsequent to atropine (mean 248 ms, $p < 0{\cdot}001$), were of lesser magnitude. The mean cycle length after cardiac autonomic block of all patients was 791 ±34 ms ($p < 0{\cdot}01$ for comparison with resting cycle length).

In three subjects, decrease in sinus cycle length after atropine administration prevented complete determinations of other electrophysiological variables (SNRT, atrioventricular node refractory periods, and QT interval after right atrial pacing at 100 bpm).

Similar treatment enabled analysis of autonomic effects on the AH interval. The AH interval was 78 ±5 ms before drugs, and 77 ±5 ms after autonomic blockade. Vagal and sympathetic effects were of similar magnitude. Atropine decreased the AH interval by 15 ms ($p < 0{\cdot}01$) in nine subjects who received the drug first and by 13 ms ($p < 0{\cdot}05$) in another nine who had first received propranolol. Propranolol increased the AH interval by 11 ms

($p < 0.05$) in those nine subjects who received the drug first, and by 14 ms ($p < 0.05$) in the seven subjects who had already received atropine. The durations of the His bundle electrogram (19 ± 1·2 ms) and the HV interval (44 ± 2·5 ms) were unchanged by administration of either drug.

SINUS NODE RECOVERY TIMES

There was no significant difference in sinus node recovery time after atrial pacing at 100 and 130 bpm, either before or after cardiac autonomic block. In Fig. 2, the effects of cardiac autonomic block on sinus node recovery time are shown. Atropine significantly decreased sinus node recovery time by approximately 497 and 398 ms with pacing at 100 and 130 bpm, respectively, and in patients who had first received propranolol, by 320 and 291 ms at 100 and 130 bpm, respectively ($p < 0.001$ for all four treatments). Propranolol administration increased sinus node recovery time by 80 ms (NS) and 118 ms ($p < 0.025$), with pacing at 100 and 130 bpm, respectively, and in patients who had first received atropine, by 314 ms ($p < 0.025$) and 289 ms ($p < 0.001$) at 100 and 130 bpm, respectively. Vagal effects on sinus node recovery time, assessed by changes occurring after atropine administration, were therefore of greater magnitude than sympathetic effects, measured by changes after propranolol. Thus, sinus node recovery time after autonomic block was 928 ± 42 ms at 100 bpm and 955 ± 40 ms at 130 bpm, both significantly less than before drugs ($p < 0.001$ and $p < 0.005$, respectively).

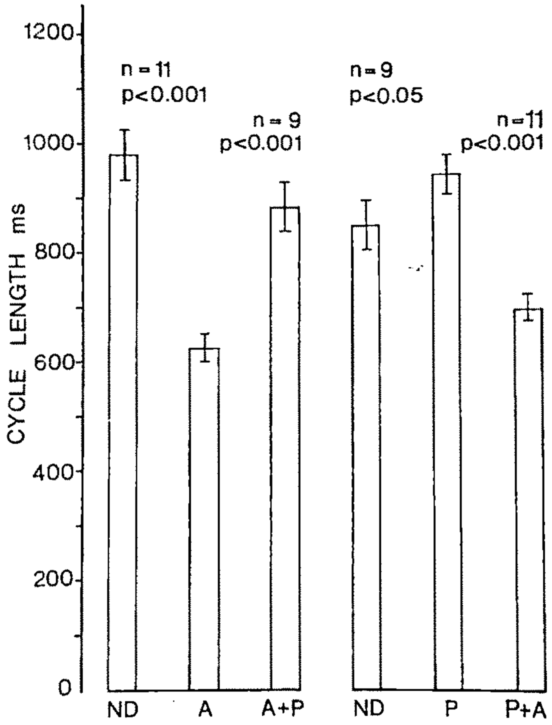

Fig. 1 *Sinus cycle length before and after administration of first atropine (A) and then propranolol (P)* (to left) *and of first propranolol and then atropine* (to right). *The number of subjects (n) and significance levels for each treatment period are shown.*

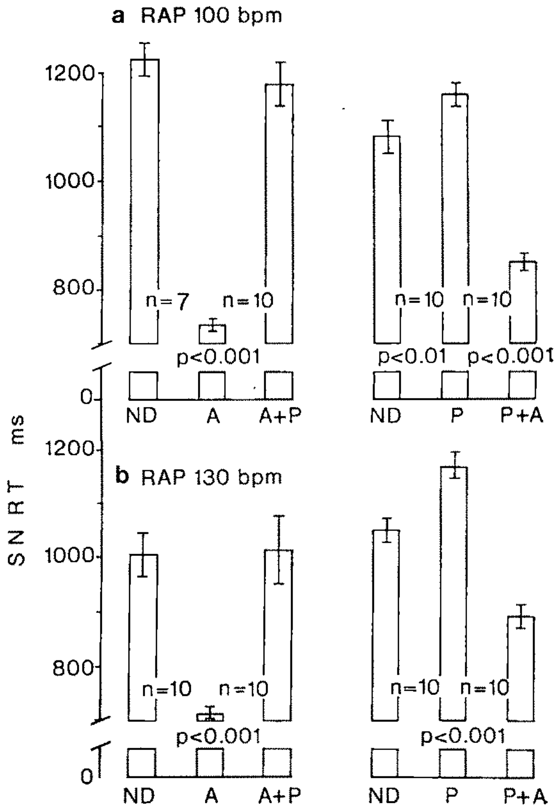

Fig. 2 *Sinus node recovery time (SNRT) before and after autonomic block. SNRT was assessed after right atrial pacing (RAP) at 100 bpm* (a) *and 130 bpm* (b).

WENCKEBACH THRESHOLD TO RIGHT ATRIAL PACING

In the 16 patients studied, the right atrial pacing rate at which atrioventricular node Wenckebach developed (157 ± 7 bpm) was no different after administration of atropine and propranolol (158 ± 6 bpm). Vagal and sympathetic effects respectively increased and decreased the Wenckebach threshold by approximately 20 to 29 bpm ($p < 0.05$ for all treatments).

REFRACTORY PERIODS

There were no significant effects of atropine or propranolol on atrial effective refractory periods (ERP) (245 ±27 ms) in the 16 subjects tested. Exact determinations of the relative refractory period of the intraventricular conduction system were limited in all subjects by the functional refractory period (FRP) of the atrioventricular node. Because of this, autonomic effects on refractory periods of the intraventricular conduction system could not be assessed.

The effective and functional refractory periods of the atrioventricular node were determined at the same basic pacing rate (100 bpm) in 12 subjects. In these, the effective refractory period of the atrioventricular node was decreased by atropine by 43 ms (those receiving atropine first) and by 55 ms (those receiving propranolol first) ($p < 0{\cdot}05$ for both treatments). No significant effects of propranolol were, however, demonstrated. Similarly, only significant vagal effects on the functional refractory period of the atrioventricular node were shown. The functional refractory period of the atrioventricular node was 408 ±19 ms before drugs. This was decreased by 55 ms ($p < 0{\cdot}05$) in those initially receiving atropine, and by 41 ms ($p < 0{\cdot}05$) in those receiving atropine subsequent to propranolol.

QT INTERVAL

The QT interval was significantly longer with pacing at 100 bpm (334 ±3 ms) than at 130 bpm (314 ±4 ms) ($p < 0{\cdot}001$). This difference persisted after autonomic block. Atropine was shown to decrease significantly the QT interval with pacing at 100 bpm ($p < 0{\cdot}01$) but not at 130 bpm (Fig. 3). No significant effects resulted from propranolol administration.

Discussion

The doses of atropine and propranolol chosen to induce vagal and sympathetic block were 75 per cent of those thought to be necessary to completely block autonomic effects on heart rate.[11] The difference in intrinsic heart rate in our subjects from those reported by Jose presumably may reflect these different doses. It is planned to compare this normal cohort with patients with disordered function of the sinuatrial and atrioventricular nodes to develop more sophisticated criteria for recognition of abnormalities. Because of this, these lesser doses were chosen after preliminary studies as appropriate to minimise side effects in patients often of advanced age and with other cardiac disease. Other effects of atropine and propranolol, such as antagonism of the nicotinic action of acetylcholine at autonomic ganglia and production of a degree of cardiac sympathetic block by atropine,[15] and direct and reflex cardiac effects after peripheral adrenergic blockade by propranolol,[16] were assumed to be unimportant.

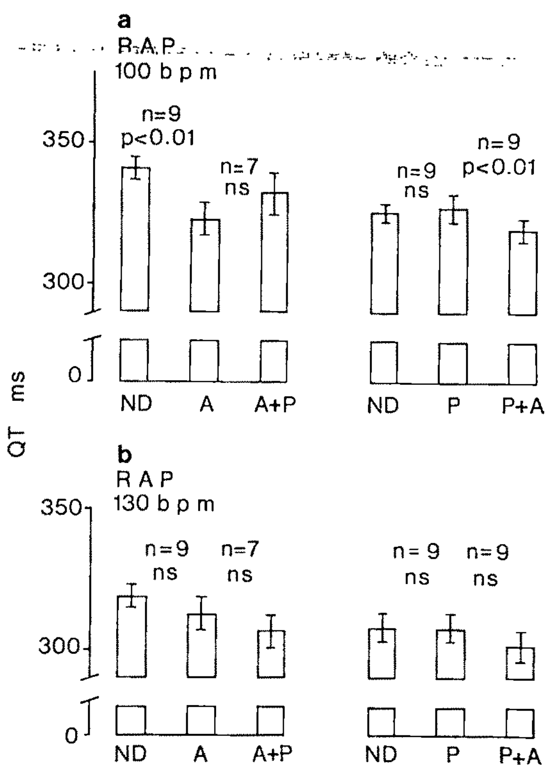

Fig. 3 *QT interval before and after autonomic block. Determinations are shown at right atrial pacing (RAP) rates of 100 bpm* (a) *and 130 bpm* (b).

The choice as to whether atropine or propranolol was initially administered was not randomised. Instead, those patients with an initially longer sinus cycle length usually received atropine first. This attempted to minimise the incidence of tachycardia after atropine which would preclude determination of sinus node recovery time and refractory periods at an atrial pacing rate of 100 bpm. However, those patients with an initially longer cycle length before drugs had a longer cycle length after complete autonomic block. This suggested that the observations reflected a normal distribution of intrinsic heart rates, and that equivalent vagal and sympathetic block was probably achieved.

Autonomic effects on sinuatrial node function can be judged from examination of the effects of atropine and propranolol on cycle length and sinus node recovery time. For both variables, though both vagal and sympathetic effects were significant and opposing, vagal influences were greater. These effects on cycle length have long been recognised.[17–19] Other electrophysiology groups[20 21] have examined autonomic influences on cycle length and sinus node recovery time in patients with sick sinus syndrome. They showed a diminished responsiveness of sinus cycle length and a distinct decrease[20] in sinus node recovery time after atropine administration. Isoprenaline rather than propranolol was used to test sympathetic effects in these studies, both normal[20] and subnormal[21] increase in sinus cycle length being reported. Though no normal controls were included in these studies, prolongation of the sinus node cycle length and corrected sinus node recovery time in normal subjects by 0·1 mg/kg propranolol have recently been reported.[22] The vagal influence on normal sinus node recovery time has also been shown.[23] However, in this study, a variable dose of atropine was given (1 to 2 mg, according to age) making quantitative analysis difficult. The decrease in sinus node recovery time after atropine may reflect not only enhanced automaticity, but a decrease in sinuatrial conduction time.[23] Indeed, occasionally a paradoxical lengthening of sinus node recovery time is observed after atropine.[24] This presumably reflects reversal of sinuatrial entrance block and more complete suppression of the sinuatrial node with pacing. This was not observed in any of our patients.

No significant change in effective refractory period of the atrium was shown after autonomic block. Previous reports have been conflicting.[23 25] It may be surmised that any effects are probably small.

Vagal and sympathetic effects on two variables of atrioventricular node function, AH interval and Wenckebach threshold, were counterbalancing. In absolute magnitude, the changes after either drug were relatively small. The observed normal values for effective and for functional refractory periods of the atrioventricular node are in close agreement with previously published results.[12] Refractory periods of the atrioventricular node, however, were shown to be subject only to significant vagal effects. By contrast, Seides *et al.*[26] were able to show a significant increase of the effective and functional refactory period of the atrioventricular node after the administration of intravenous propranolol (0·1 mg/kg). The explanation for the lack of demonstration of significant sympathetic effects in the present study, using a larger dose, is unclear.

The aspects of intraventricular conduction studied were the HV interval and relative refractory period. No statement as to autonomic effects on the refractory periods can be made from the present study. However, the absence of effect of atropine[25] and propranolol[26] on HV interval agrees with previous findings.

The observed effects of the drugs on the QT interval are clinically relevant. Variability of the QT interval is well recognised, but studies of the effects of autonomic interactions have been conflicting.[27] Beta-adrenoreceptor blocking agents are advocated to decrease QT in the treatment of ventricular arrhythmias associated with hereditary or drug-induced QT prolongation.[28] Paradoxically, isoprenaline is recommended for the treatment of *torsade de pointes*, a ventricular tachyarrhythmia associated with QT prolongation.[29] Anatomically, the opposing effects of right and left stellate nerve stimulation on the QT interval in experimental animals have been noted.[30] This present procedure showed only small though statistically significant vagal effects on the normal QT interval, and no demonstrable changes after propranolol. Further examination of autonomic effects on the QT interval are apparently necessary.

CLINICAL IMPLICATIONS

This study has demonstrated significant vagal and sympathetic effects on clinical electrophysiological variables in a group of normal subjects. The implications for the need for measurement of these variables under steady state conditions, while patients are not subjected to factors such as pain and anxiety, are readily apparent. It is anticipated that abolition of autonomic influences might aid recognition of abnormal pathological conditions as distinct from variable physiological states. The proposition that the statistical power of the electrophysiological observations will be enhanced by autonomic blockade must, however, be examined by a prospective study comparing abnormal and control groups.

References

1 Sherlag BJ, Lau SH, Helfant RH, Berkowitz WD, Stein E, Damato AN. Catheter technique for recording His bundle activity in man. *Circulation* 1969; **39:** 13–8.

2 Wit AL, Weiss MB, Berkowitz WD, Rosen KM, Steiner C, Damato AN. Patterns of atrioventricular conduction in the human heart. *Circ Res* 1970; **27:** 345–59.

3 Wellens HJJ. *Electrical stimulation of the heart in the study and treatment of tachycardias.* Baltimore: University Park Press, 1971: 14–26.

4 Ferrer MI. The sick sinus syndrome. *Circulation* 1973; **47:** 635–41.

5 Puech P. Atrioventricular block: the value of intracardiac recordings. In: Krikler DM, Goodwin JF, eds. *Cardiac arrhythmias.* Philadelphia: WB Saunders, 1975: 81–115.

6 Mandel W, Hayakawa H, Danzig R, Marcus HS. Evaluation of sinoatrial node function in man by overdrive suppression. *Circulation* 1971; **44:** 59–66.

7 Narula OS, Samet P, Javier RP. Significance of the sinus-node recovery time. *Circulation* 1972; **45:** 140–58.

8 Strauss HC, Saroff AL, Bigger JT Jr, Giardina EGV. Premature atrial stimulation as a key to understanding of sinoatrial conduction in man. *Circulation* 1973; **47:** 86–93.

9 Bisset JK, Kane JJ, de Soyza H, Murphy ML. Electrophysiological significance of rapid atrial pacing as a test of atrioventricular conduction. *Cardiovasc Res* 1975; **9:** 593–9.

10 Jose AD, Taylor RR. Autonomic blockade by propranolol and atropine to study intrinsic myocardial function in man. *J Clin Invest* 1969; **48:** 2019–31.

11 Jose AD. Effect of combined sympathetic and parasympathetic blockade on heart rate and cardiac function in man. *Am J Cardiol* 1966; **18:** 476–8.

12 Denes P, Wu D, Dhingra R, Pietras RJ, Rosen KM The effect of cycle length on cardiac refractory periods in man. *Circulation* 1974; **49:** 32–41.

13 Bazett HC. An analysis of the time relations of electrocardiograms. *Heart (London)* 1918–20; **7:** 353–70.

14 Lepeschkin E, Surawicz B. The measurement of the QT interval of the electrocardiogram. *Circulation* 1952; **6:** 378–88.

15 Brown AM. Cardiac sympathetic adrenergic pathways in which synaptic transmission is blocked by atropine sulphate. *J Physiol (Lond)* 1967; **191:** 271–9.

16 Korner PI. Role of the autonomic nervous system in reflex cardiovascular control. *Prog Cardiol* 1978; **7:** 55–101.

17 Levy MN. Sympathetic-parasympathetic interactions in the heart. *Circ Res* 1971; **29:** 437–45.

18 Scher AM, Ohm WW, Bumgarner K, Boynton R, Young AC. Sympathetic and parasympathetic control of heart rate in the dog, baboon, and man. *Fed Proc* 1972; **31:** 1219–25.

19 Glick G, Braunwald E. Relative roles of the sympathetic and parasympathetic nervous system in the reflex control of the heart rate. *Circ Res* 1965; **16:** 363–75.

20 Strauss HC, Bigger JT, Saroff AL, Giardina EG. Electrophysiologic evaluation of sinus node function in patients with sinus node dysfunction. *Circulation* 1976; **53:** 763–76.

21 Mandel WJ, Hayakawa H, Allen HN, Danzig R, Kermaier AI. Assessment of sinus node function in patients with the sick sinus syndrome. *Circulation* 1972; **46:** 761–9.

22 Vasquez M, Chuquimia R, Shantha N, Khan M, Narula OS. Clinical electrophysiological effects of propranolol on normal sinus node function. *Br Heart J* 1979; **41:** 709–15.

23 Dhingra R, Amat-Y-Leon F, Wyndham C, *et al.* Electrophysiologic effects of atropine on human sinus node and atrium. *Am J Cardiol* 1976; **38:** 429–34.

24 Bashour T, Hemb R, Wicramesekaran R. An unusual effect of atropine on overdrive suppression. *Circulation* 1973; **48:** 911.

25 Akhtar M, Damato AN, Caracta AR, Batsford WD, Josephson ME, Lau SH. Electrophysiologic effect of atropine on atrioventricular conduction studied by His bundle electrogram. *Am J Cardiol* 1974; **33:** 333–43.

26 Seides SF, Josephson ME, Batsford WP, Weisfogel GM, Lau SH, Damato AN. The electrophysiology of propranolol in man. *Am Heart J* 1974; **88:** 733–41.

27 Abildskov JA. Adrenergic effects on the QT interval of the electrocardiogram. *Am Heart J* 1976; **92:** 210–6.

28 Schwartz PJ, Periti M, Malliani A. The long QT syndrome. *Am Heart J* 1976; **89:** 378–90.

29 Krikler DM, Curry PV. *Torsade de pointes,* an atypical ventricular tachycardia. *Br Heart J* 1976; **38:** 117–20.

30 Yanowitz F, Preston JB, Abildskov JA. Functional distribution of right and left stellate innervation to the ventricles: production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone. *Circ Res* 1966; **18:** 416–28.

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Effect of intracoronary glyceryl trinitrate on perfusion distribution in the collateralised human myocardium

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SUMMARY The effect on myocardial perfusion distribution of intracoronary glyceryl trinitrate in a dose (60 μg) insufficient to cause alterations in systemic blood pressure or heart rate was studied in eight patients with angiographically demonstrated collaterals from the left coronary system to the distal right coronary artery. Double isotope imaging using technetium-99m and iodine-131 labelled albumin macroaggregates allowed each patient to serve as his own control. The reproducibility of the imaging and data handling techniques was shown in 12 control patients. Glyceryl trinitrate caused a significant diminution in the collateral-mediated fractional perfusion while increasing that of the native coronary bed.

While there is general agreement about its peripheral actions, the direct effects of glyceryl trinitrate on collateral vessel mediated myocardial perfusion remain controversial.[1–3] Experimental,[1,2,4] and intraoperative[5] pressure and flow measurements, though providing useful data about the functional behaviour of the collateral bed, do not allow direct conclusions regarding myocardial perfusion. In this study myocardial imaging after intracoronary injections of technetium-99m and iodine-131 labelled human albumin macroaggregates was used to determine the effect of intracoronary glyceryl trinitrate on myocardial perfusion distribution in eight patients with angiographically demonstrable left-to-right collaterals. The double isotope technique allowed each patient to serve as his own control.

Subjects and methods

PATIENT POPULATION

The study group consisted of eight patients (seven men, one woman) with a history of myocardial infarction six or more months previously, who were submitted to selective coronary arteriography because of angina. Left ventriculography and selective coronary arteriography were performed using Renografin-76. Selective arteriography was performed using Judkins coronary catheters introduced percutaneously into the femoral artery by the Seldinger technique. Each patient's entry into the study was decided at the time of arteriography and was based on opacification of the distal right coronary artery via angiographically visible collateral vessels during selective injections of the left coronary system. All patients had either total (100%) or subtotal (99%) occlusion of the right coronary artery. Seven of the eight patients also had significant (50%) obstruction of the left anterior descending coronary artery and three of these had circumflex lesions as well.

STUDY PROCEDURE

The procedure was designed to allow each patient to serve as his own control. After completion of left ventriculography and selective coronary arteriography, 10 minutes were allowed to elapse before injection of the macroaggregates. Previous studies have shown[6] that contrast medium-induced hyperaemia subsides well within this time. Human albumin macroaggregates (mean particle diameter 10 to 40 μ) labelled with either 500 μC technetium-99m (^{99m}Tc) or 100 μC iodine-131 (^{131}I) suspended in 2 ml normal saline were used in each study. The order in which the two isotopes were administered was randomly chosen. The macroaggregate suspension was well agitated before injection. After each injection the coronary catheter was flushed with 2 ml heparinised saline. Seconds

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after injection of the first isotope into the left coronary artery, glyceryl trinitrate 60 μg was injected after which the catheter was withdrawn from the coronary ostium. The aortic pressure and heart rate were continuously monitored throughout the procedure. Thirty seconds after the glyceryl trinitrate injection, the catheter was repositioned in the left coronary ostium and the macroaggregate suspension bearing the second isotope was injected. Approximately 10 minutes after completion of the above procedures, simultaneous dual isotope myocardial imaging in the anterior, 45° right and left anterior oblique (RAO and LAO), and left lateral views was performed using an Ohio Nuclear dual probe rectilinear scanner with 20 per cent energy windows around peaks at 140 and 370 kV. Digital counts over a 64 × 64 matrix from each image were stored on magnetic tape.

Twelve other patients underwent an identical study procedure but received 2 ml normal saline instead of glyceryl trinitrate. They served as controls for the validation of the dual isotope technique and the subsequent quantitative image analysis.

ANALYSIS OF RESULTS

Colour isocount displays were reconstructed on an oscilloscope by retrieving the digitised data stored during scintiscanning. Orthogonal matrices composed of 7 × 4 and 6 × 4 square cells were superimposed on right and left anterior oblique images, respectively. The matrices were centred around the cardiac contour and were positioned identically over the two isotope images. The fraction of digital counts within each matrix element relative to the total counts over the whole matrix was calculated and expressed as a percentage.

Triads of matrix elements deemed to overlie myocardial regions perfused largely by one of the three major coronary arterial systems were chosen as depicted in the Figure. In the right anterior oblique view, regions perfused by the left anterior descending and right coronary artery were chosen in a manner that excluded intermediate areas in which the source of perfusion may have been overlapping. Matrix elements close to the lateral borders were probably outside the cardiac silhouette as evidenced by the low fractional counts (< 1·0%) within them. Since part of the region assigned to the right coronary artery distribution in this view may have been overlying the circumflex distribution, left anterior oblique views were also analysed. In this projection the left anterior descending and circumflex distributions assumed an anteroposterior separation which permitted their individual analysis.

Since imaging through the energy windows corresponding to the two isotopes was performed simultaneously, a strict one-to-one correspondence was ensured between matrix elements of the two images obtained. Accordingly, paired Student's t tests were performed to assess the statistical significance of changes of fractional counts within the above-described triads of matrix elements.

Identical data handling and statistical analysis were applied to the images from patients in the control group.

Results

Intracoronary injections of glyceryl trinitrate in the doses used in this study caused no alterations in aortic blood pressure (systolic, diastolic, or mean) or heart rate. There were no complications in any of the eight patients during, or as a result of the study procedure.

The results of the statistical analysis described in the previous section are summarised in the Table. In the overall group of eight patients, each triad of matrix elements yielded 24 pairs of fractional distribution. Statistical analysis of these data (Table) showed that after intracoronary glyceryl trinitrate

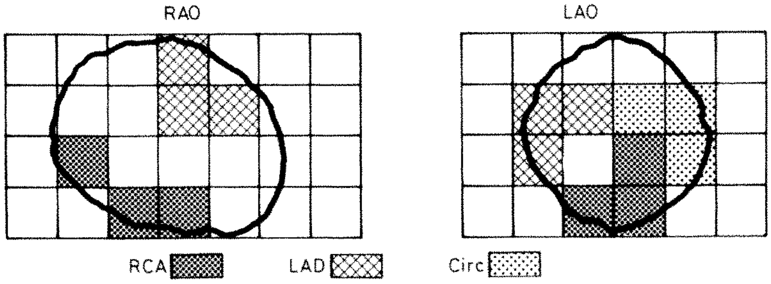

Fig. *Analysis of myocardial perfusion images. Orthogonal matrices were superimposed on 45° right anterior oblique (RAO) and left anterior oblique (LAO) images. Triads of matrix elements were assigned, as illustrated, to represent regional perfusion in the distribution of the right (RCA), left anterior descending (LAD), and circumflex (Circ) coronary arteries.*

Table *Summary of statistical data* analysis†*

View	*Coronary distribution*	*No.*	*Control (%)*	*After glyceryl trinitrate*	*Significance of difference*
Right anterior oblique	Left anterior descending	24	6·87 ±0·38	7·90 ±0·46	$p < 0{\cdot}01$
	Right coronary artery	24	3·49 ±0·22	2·95 ±0·21	$p < 0{\cdot}001$
Left anterior oblique	Left anterior descending	24	5·86 ±0·53	6·71 ±0·67	$p < 0{\cdot}01$
	Circumflex	24	7·19 ±0·57	6·90 ±0·65	$p > 0{\cdot}05$
	Right coronary artery	24	7·33 ±0·62	6·61 ±0·59	$p < 0{\cdot}05$

* Fractional perfusion expressed as mean per cent of total counts ±SE. † Paired Student's t test.

there was a significant fall in the proportion of the total left coronary perfusion distributed by collateral vessels to the right coronary artery region ($p < 0{\cdot}001$ from right anterior oblique views, $p < 0{\cdot}05$ from left anterior oblique views). At the same time the proportion of perfusion in the left anterior descending distribution increased significantly after glyceryl trinitrate ($p < 0{\cdot}01$ from right anterior oblique views, $p < 0{\cdot}01$ from left anterior oblique views). There was no significant change in the proportional perfusion of the circumflex distribution ($p > 0{\cdot}05$) as analysed from left anterior oblique views. Thus, the circumflex distribution could not have contributed to the very significant differences within regions assigned to the right coronary artery distribution in the right anterior oblique views.

Analysis of imaging data obtained from the 12 control patients showed no statistical difference ($p > 0{\cdot}05$) in the fractional perfusion of any of the coronary arterial distributions as assessed by the two isotopes injected before and after saline. These findings validated the reproducibility of the method and analysis of data used in this study with respect to the two isotopes.

Discussion

The use of intracoronary injections of radioactive labelled human albumin macroaggregates, first reported by Ashburn *et al.*,[7] has been shown to be both a valid and safe technique of assessing myocardial perfusion distribution.[8, 9] A double isotope technique using indium-113m and ^{99m}Tc-macroaggregated albumin was first used by Ritchie *et al.*[6] to compare the regional myocardial perfusion distributions before and after stress-induced ischaemia.

Intracoronary glyceryl trinitrate in the dosage used in this study (60 μg) produced no significant alterations in systemic blood pressure or heart rate. Thus, the technique allowed observations to be made about the action of glyceryl trinitrate on the coronary circulation independently of its peripheral actions. The group of control patients showed that the technique of dual isotope imaging as well as the data analysis yielded statistically reproducible estimates of segmental myocardial perfusion using the two isotopes. We felt it important to validate this point since selective injections into the branches of the left main coronary artery could conceivably occur either by virtue of physical entry of the catheter tip into one of the branches in patients with a short left main segment or streaming of the injectate under pressure without adequate mixing. The application of the procedure to the control patients did not rule out this possibility but did demonstrate that if the catheter is removed from the coronary ostium and then reinserted by the same operator using the same technique, the catheter position is reproducible between injections and, therefore, similar injections result in reproducible macroaggregate distributions. The use of each patient as his own control made it possible to analyse the data in a paired fashion minimising interindividual differences in coronary perfusion distribution and focusing attention on the changes induced by glyceryl trinitrate.

It is important to point out that this technique does not allow estimation of absolute myocardial perfusion and that our findings concern only the proportional distribution of the total flow. Experimental studies previously reported on the direct effects of glyceryl trinitrate on collateral perfusion have been contradictory.[1–3] The contradictions, however, were among studies performed by very different techniques and, therefore, not really comparable. Peripheral coronary pressure from regions distal to ligation of the left anterior descending artery in dogs has been shown to increase significantly after administration of glyceryl trinitrate.[1, 2, 4] Studies in humans at the time of coronary artery bypass surgery showed a similar increase in peripheral coronary pressure and, more importantly, the calculated resistance of the collateral bed was found to decrease significantly in response to glyceryl trinitrate.[5] It is important to point out that the resistance of the native coronary bed was not simultaneously measured and may decrease even more. This would result in a shift of fractional distribution in a manner favouring the native coronary bed and away from the collateral bed. It is possible that despite the relatively small decrease in fractional distribution to the collateralised area shown in our study (usually 10%) the absolute perfusion of these regions in terms of ml/min per 100 g myocardium may in fact have increased but to a lesser degree than a simultaneous increase to the region supplied by the left anterior descending artery. Ganz and Marcus[3] have found that the efficacy of glyceryl trinitrate in the relief of angina induced by pacing in patients in whom the blood pressure was not allowed to respond to glyceryl trinitrate was severely limited. These authors concluded that the effect of glyceryl trinitrate on the coronary circulation was a relatively minor component of its beneficial effect in ischaemia. Cohen *et al.*[10] reported that the administration of a coronary vasodilator (isoprenaline) after acute coronary occlusion in dogs resulted in a shift in myocardial perfusion away from regions supplied by collateral vessels. As in other dog experiments, however, the behaviour of the collateral circulation may be very different from that in the human since collateral vessels are known to be readily available in the acute setting in dogs while in humans collaterals are believed to develop slowly over long periods of time in response to chronic ischaemia. Collaterals which develop in this manner may have different vasoreactivity from those which are present in the dog in the absence of chronic ischaemia.

The observed effect of glyceryl trinitrate on myocardial perfusion distribution in the collateralised human heart implies a lesser responsiveness of the collateral circulatory bed to the dilatatory effect of glyceryl trinitrate compared with the native coronary circulation. This could be the result of either an intrinsic difference in the sensitivity of the resistive elements in the two circulations or ischaemia-mediated dilatation in the former which might pre-empt a portion of the maximal inducible dilatatory response.[11] Our observations support previous findings that the effect of glyceryl trinitrate on the coronary circulation is a relatively minor component of its beneficial effects in ischaemia.[2 3] If absolute coronary flow does not increase, the direct effect of glyceryl trinitrate on myocardial perfusion distribution may be detrimental but could still be overridden by its beneficial systemic actions. Further studies will be required to elucidate the reasons for these differences in glyceryl trinitrate responsiveness. Such studies might improve our understanding about the physiological behaviour of the collateral circulation and permit interventions aimed at maximising its beneficial function in ischaemic heart disease.

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References

1 Fam WM, McGregor M. Effect of coronary vasodilator drugs on retrograde flow in areas of myocardial ischaemia. *Circ Res* 1964; **15:** 355–65.

2 Weisse AB, Senft A, Khan MI, Regan TJ. Effect of nitrate infusions on the systemic and coronary circulations following acute experimental myocardial infarction in the intact dog. *Am J Cardiol* 1972; **30:** 362–70.

3 Ganz W, Marcus HS. Failure of intracoronary nitroglycerin to alleviate pacing-induced angina. *Circulation* 1972; **46:** 880–9.

4 Cohen MV, Downey JM, Sonnenblick EH, Kirk ES. The effects of nitroglycerin on coronary collaterals and myocardial contractility. *J Clin Invest* 1973; **52:** 2836–47.

5 Goldstein RE, Stinson EB, Scherer JL, Seningen RP, Grehl TM, Epstein SE. Intraoperative coronary collateral function in patients with coronary occlusive disease. Nitroglycerin responsiveness and angiographic correlations. *Circulation* 1974; **49:** 298–308.

6 Ritchie JL, Hamilton GW, Gould KL, Allen D, Kennedy JW, Hammermeister KE. Myocardial imaging with indium-133m- and technetium-99m-macroaggregated albumin. *Am J Cardiol* 1975; **35:** 380–9.

7 Ashburn WL, Braunwald E, Simon AL, Peterson KL, Gault JH. Myocardial perfusion imaging with radioactive-labeled particles injected directly into the coronary circulation of patients with coronary artery disease. *Circulation* 1971; **44:** 851–65.

8 Jansen C, Judkins MP, Grames GM, Gander M, Adams R. Myocardial perfusion color scintigraphy with MAA. *Radiology* 1973; **109:** 369–80.

9 Grames GM, Jansen C, Gander MP, Wieland HC, Judkins MP. Safety of the direct coronary injection of radiolabeled particles. *J Nucl Med* 1974; **15:** 2–6.

10 Cohen MV, Sonnenblick EH, Kirk ES. Coronary steal: its role in deterimental effect of isoproterenol after acute coronary occlusion in dogs. *Am J Cardiol* 1976; **38:** 880–8.

11 Cohen MV, Kirk ES. Differential response of large and small coronary arteries to nitroglycerin and angiotensin: autoregulation and tachyphylaxis. *Circ Res* 1973; **33:** 445–53.

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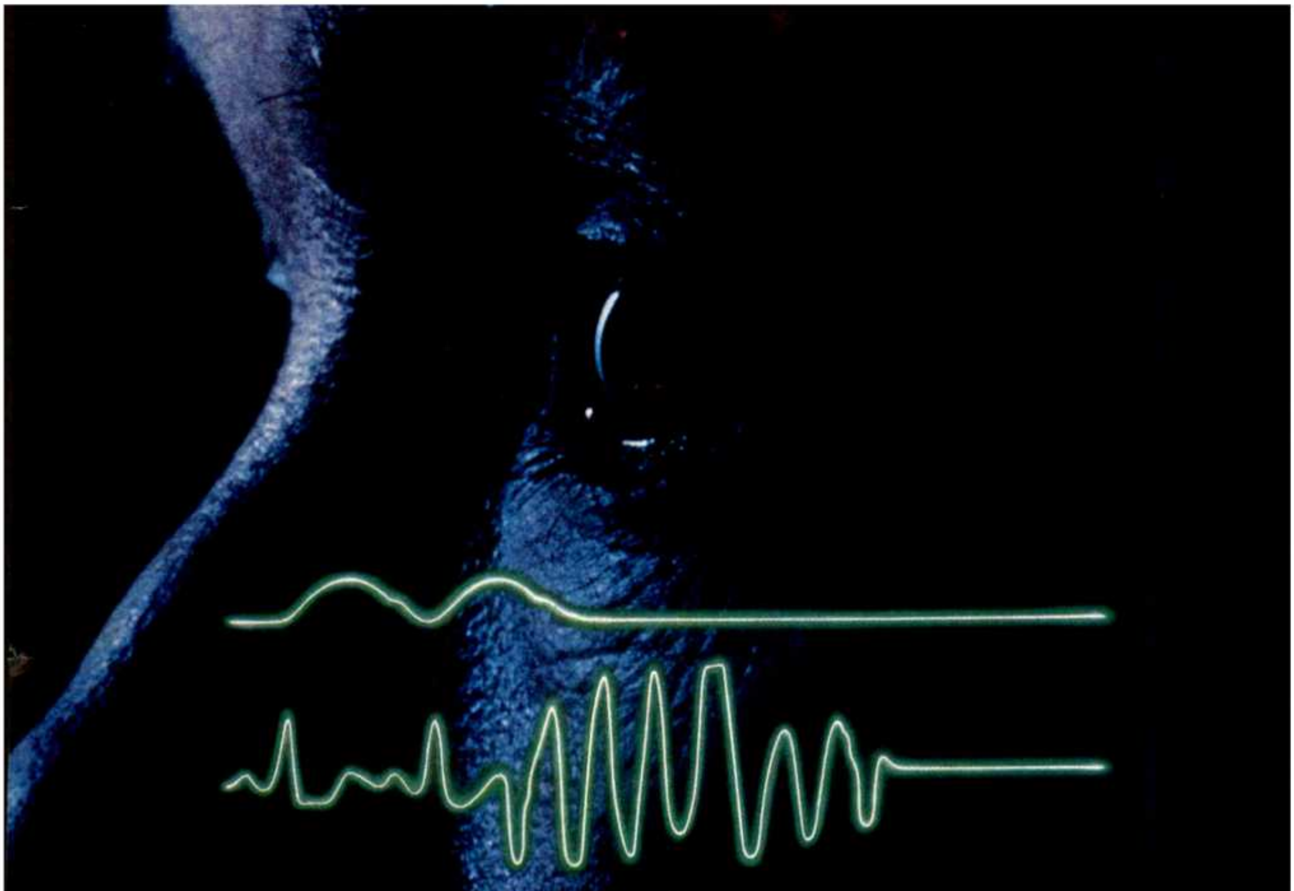

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References 1. Kannel WB, Doyle JT, McNamara PM et al. Precursors of sudden coronary death. *Circulation* 1975; 51(4): 606-613. **2.** Sundquist H, Anttila M, Simon A, Reich JW. Comparative bioavailability and pharmacokinetics of sotalol administered alone and in combination with hydrochlorothiazide. *J Clin Pharmacol* 1979; 19(8-9, pt 2): 565-570. **3.** Jaattela A. The combination of sotalol and hydrochlorothiazide in the treatment of hypertension. *J Clin Pharmacol* 1979; 19(8-9, pt 2): 557-564. **4.** Ranson W, Myburgh DP. Synerg of a beta blocker and a diuretic in the once-a-day treatment of essential hypertension. *J Clin Pharmacol* 1979; 19(8-9, pt 2): 571-578. **5.** Reynaert J. Once-a-day treatment with sotalol and hydrochlorothiazide in patients with essential hypertension. *J Clin Pharmacol* 1 19(8-9, pt 2): 579-583. **6.** Monsalvo HJ. Sotalol/hydrochlorothiazide in geriatric hypertensive patients. *J Clin Pharmacol* 1979; 19(8-9, pt 2): 584-590. *Trademark. Authorised User. Further information is available to the medical profession on request.

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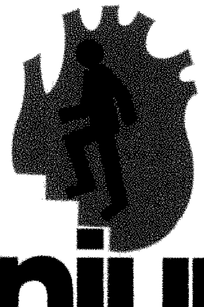

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References

1. Nayler, W.G. *Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
2. Flameng, W. *et al. Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
3. Detry, J.M.R. *et al. Eur. J. Cardiol.* **4,** 165, 1976.
4. Gobel, F.L. *et al. Am. J. Cardiol.* **37,** 139, 1976.
5. Jenkins, M.D. *et al. Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
6. Bloem, Th. J.J.M. *et al. Clin. Cardiol.* **2,** 407, 1979.
7. Shapiro, W. *Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
8. Nordstrom, L.A. *Chest,* **74,** 50, 1978.

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Effect of myocardial shortening velocity on duration of electrical and mechanical systole

S_2T interval as measure of shortening rate

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SUMMARY To determine the effect of myocardial shortening velocity on the duration of electrical and mechanical systole, five healthy men, ages 32 to 41, were studied. Carotid massage and atropine were used to define the effects of changes in heart rate without changes in shortening rate. The effects of amyl nitrite, which produced approximately the same degree of tachycardia as atropine but a significantly higher maximum shortening rate, were compared with those of atropine to assess the effects of faster shortening velocities. The increased heart rate produced by both agents caused a substantial decrease in both the QT and the S_1S_2 intervals, but the QT interval was longer and the S_1S_2 interval shorter with the amyl nitrite. Thus, the S_2T interval was substantially longer after amyl nitrite. The results are in keeping with the finding in isolated cardiac muscle that active shortening increases action potential duration and decreases the duration of mechanical activation. These observations raise the possibility that longer QT intervals and shorter S_1S_2 intervals would also be seen in patients with hypokinetic ventricular segments when the healthy muscle contracts more vigorously to compensate for the weaker segments.

Active shortening of isolated cardiac muscle increases the action potential duration,[1] and decreases the duration of mechanical activity.[2 3] These observations suggest that the electrocardiographically recorded T waves in man might occur later and second heart sounds (S_2) earlier, when ventricular ejection rate increases. If this is so, the interval between the two might be used as an index of myocardial fibre shortening rate. This hypothesis was tested in five healthy volunteers using carotid massage and atropine to define the changes that occur in the time intervals with variation in heart rate but without large changes in fibre shortening. Amyl nitrite was used to increase the velocity of ventricular ejection, and the results obtained with this agent were compared with those during the tachycardia produced by atropine. Myocardial shortening rate was assessed from simultaneous echocardiograms.

Methods

Five healthy, non-obese men, ages 32 to 41 years, were studied. All were without heart disease and all participated to some degree in regular athletics. They were asked to hold their breath at end expiration during the periods of recording to increase uniformity of conditions and to minimise respiratory interference.

RECORDING

M-mode echocardiograms were obtained with a Unirad 100 Series Echoscope. Left ventricular contraction was measured at a point just below the mitral valve. Simultaneous phonocardiogram, lead II electrocardiogram, and differentiated electrocardiographic traces were displayed on the same recording (Fig. 1). Lead II was used throughout since the T wave vector was closest to this lead in every subject. The use of a single electrocardiograph lead to determine the beginning of the QRS complex and the end of the T wave is justified if the axis of these initial and terminal vectors do not change, as was found in the five subjects studied here. The recorder was run at 78 mm/s (nominal 75 mm/s).

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* Dr Ford is an established investigator at the American Heart Association.

† Dr Campbell performed this work during his tenure as a Sir Samuel Haslett Brown travelling scholar.

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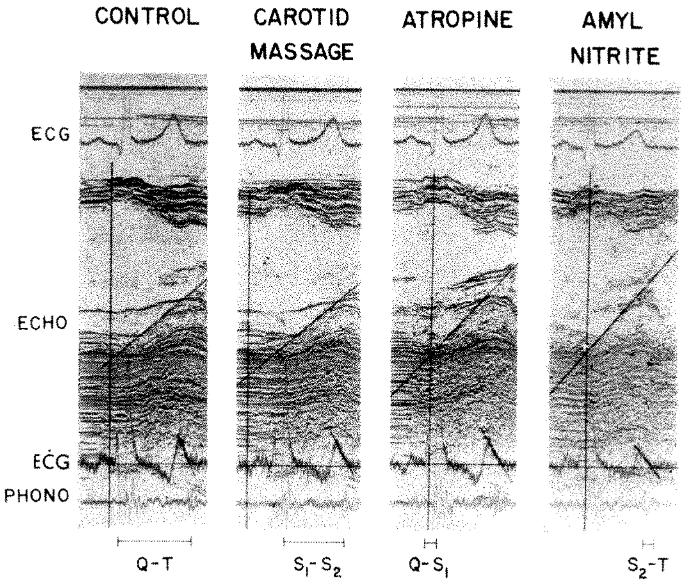

Fig. 1 *Recordings and interventions: The end of the T wave was determined as the intersection of the two lines drawn through the differentiated electrocardiographic trace (EĊG). The phonocardiogram had high and low pass filters set at 100 and 1400 Hz, respectively, throughout all studies. Relative changes in maximum fibre shortening were assessed from the slope of a line drawn through the fastest-moving component of the posterior wall echo. The lines shown here have been darkened for contrast, and obscure some of these echoes.*

MEASUREMENTS

Lines were drawn through the zero baseline of the differentiated electrocardiograph trace and through the terminal portion of the T wave on this trace as it approached the baseline (Fig. 1). The end of the T wave was taken as the intersection of these two lines. The timing of the heart sound was taken as the first high frequency component in the phonocardiogram. A vertical line through the timing marks on the record (Fig. 1) served both as a time reference for intervals on different traces and as a vertical reference for measuring the slope of posterior wall motion in the echocardiogram. Measurements of time intervals were made with dial gauge callipers (Mitutoya Co, Japan) read to the nearest 0·1 mm (1·3 ms). Most measurements were made only once. When 34 measurements made independently by two observers were compared, 23 had differences $\leqslant 0{\cdot}2$ mm. The following five intervals were measured: RR, QT, S_1S_2, QS_1, and S_2T.

Maximum myocardial shortening rate was estimated by drawing a tangent to the fastest-moving component of the posterior wall echo (Fig. 1) and computing the cotangent of the angle between this line and the vertical reference. The slopes indicate only relative changes in rate, not absolute values. Consequently, shortening rate is expressed in terms of percentage changes with each intervention, relative to the control. The end-diastolic and end-systolic diameters were measured respectively as the dimensions at the peak of the R wave and the maximum anterior movement of the posterior wall.

Posterior wall motion was chosen to indicate relative changes in maximum myocardial shortening mainly for simplicity. It required only a single measurement, that of an angle. Other indices, such as mean circumferential shortening, require several measurements, which increase the error of the estimate. Posterior wall motion has the added advantage that it reflects maximum rather than mean shortening velocity. It has the disadvantage that it results partly from circumferential fibre shortening and partly from overall movement of the left ventricle. Consequently, it does not indicate absolute myocardial shortening rate directly. It is assumed here, however, that ventricular movement was proportional to myocardial shortening in each individual in the same position. To the extent that this assumption is correct, the effects of ventricular movement cancel when calculating relative changes in velocity.

INTERVENTIONS

All recordings for each subject were made at a single time with the subject lying supine, his right side slightly raised, and with the echo transducer in the same position throughout. The order of the interventions was as follows. First a control recording was made with the subject lying quietly. Carotid massage was then applied several times to slow the pulse transiently. Next, the subject inhaled amyl nitrite, and recordings were made during the resulting tachycardia. Ten to 15 minutes later, when the tachycardia and flushing had subsided, 1·2 mg atropine was injected intravenously. Recordings were made during the peak of the ensuing tachycardia.

ANALYSIS

Measurements of 10 cardiac cycles were made for each intervention. The cycles chosen were those 10 that showed the greatest change in RR interval in response to the intervention, after excluding any record that could not be read because of respiratory interference. All measurements of the 10 cycles were averaged and the standard error of the mean computed. The size of the symbols along the Y axis in Fig. 2 and 3 (27 ms) was chosen so that of the 80 time intervals plotted, 68 had standard errors smaller than the symbols, and 18 had standard errors less than half the size of the symbols. Unless otherwise stated, significance of differences was calculated from the paired Student's t test taking the mean of 10 measurements for each individual as a single value. Those p values less than 0·05 were considered significant.

Results

The resting pulse rates ranged from 49 to 75 (mean 61). Carotid massage decreased the rates by an average of 15 per cent. Amyl nitrite increased the pulse rates by an average of 54 per cent, and atropine by 47 per cent, the difference being insignificant. The end-diastolic diameter was only slightly less with the amyl nitrite than with atropine (2·3%), but the end-systolic diameter was significantly decreased (12·5%, $p < 0{\cdot}05$). The slope of the posterior wall motion was not significantly changed by carotid massage or atropine unless the heart rate increased to about 90/min, as has been found with mean circumferential fibre shortening using atrial pacing to vary heart rate.[4] Posterior wall motion was increased significantly ($p < 0{\cdot}01$) by amyl nitrite (Fig. 2A). The large difference in posterior wall motion, compared with approximately the same change in heart rate, allowed the effects of fibre shortening to be distinguished from those of heart rate.

The QT and S_1S_2 intervals both varied inversely with heart rate (Fig. 2B and C). Close inspection of the data in Fig. 2B and C shows, however, that for each individual, the QT interval was longer for the tachycardia produced by amyl nitrite than that produced by atropine, and that the reverse is true for the S_1S_2 interval.* The shorter S_1S_2 interval and the longer QT interval with amyl nitrite as

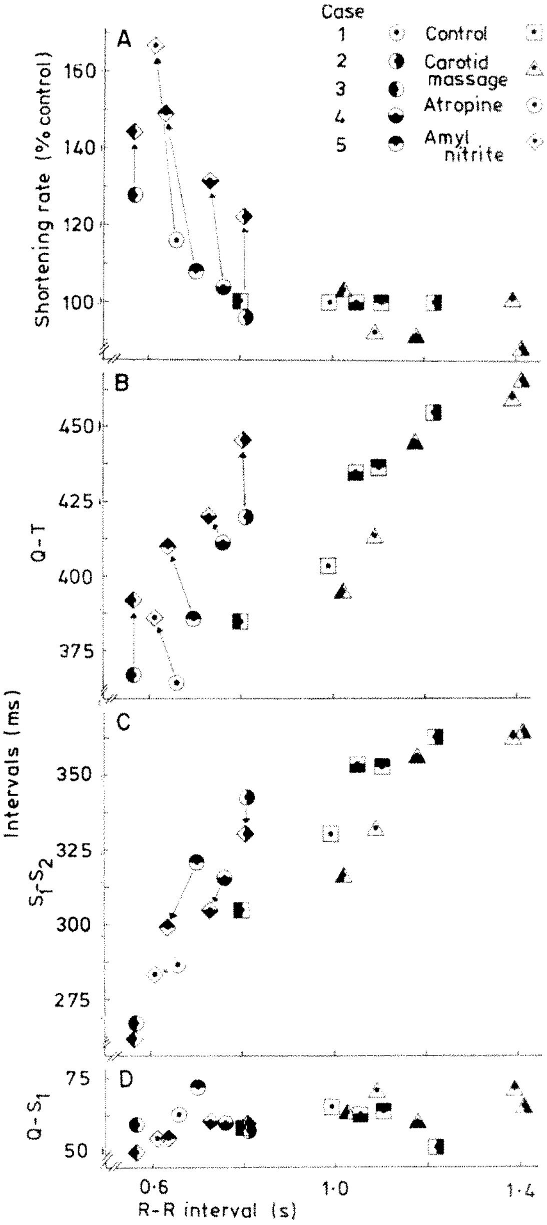

Fig. 2 *Effect of RR interval and interventions on fibre shortening and time intervals: interventions are identified by shape and subjects by shading of symbols, according to key in inset. Shortening rates (A) are expressed as a percentage of the control values. Intervals (B, C, D) as described in text. The arrows in A, B, and C indicate the direction of changes with amyl nitrite, as compared with atropine, for each subject.*

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* Three different methods of analysis showed the differences to be significant: (1) the two-tailed, paired t test gave $p < 0{\cdot}005$ for the QT and $p < 0{\cdot}03$ for the S_1S_2 intervals; (2) the probability of obtaining the intervals for all five subjects deviating in the expected direction is $1/2^5 = 1/32$, yielding $p < 0{\cdot}032$ for both the QT and S_1S_2 intervals; (3) when the unpaired t test was applied to the means for each individual, all five of the QT and three of the S_1S_2 interval differences yielded $p < 0{\cdot}05$; two of the S_1S_2 and three of the QT interval differences yielded $p < 0{\cdot}001$.

compared with atropine resulted in substantial increases in the S_2T intervals with amyl nitrite. This interval was found to correlate with changes in maximum fibre shortening, as indicated by changes in the slope of the posterior wall motion (Fig. 3A). Though the relation between fibre shortening and S_2T interval is probably not strictly linear, an estimate of the correlation between the two variables was obtained using a linear regression. For the data in Fig. 3A, the correlation coefficient was 0·67, and it was increased to 0·88 when the intervals were divided by the control values (Fig. 3B) to normalise the variation among the individuals. The S_2T interval did not correlate well with changes in heart rate.

The QS_1 interval was not significantly affected by any of the interventions (Fig. 2D), indicating that the changes in the S_2T intervals were largely the result of the changes in the QT and S_1S_2 intervals.

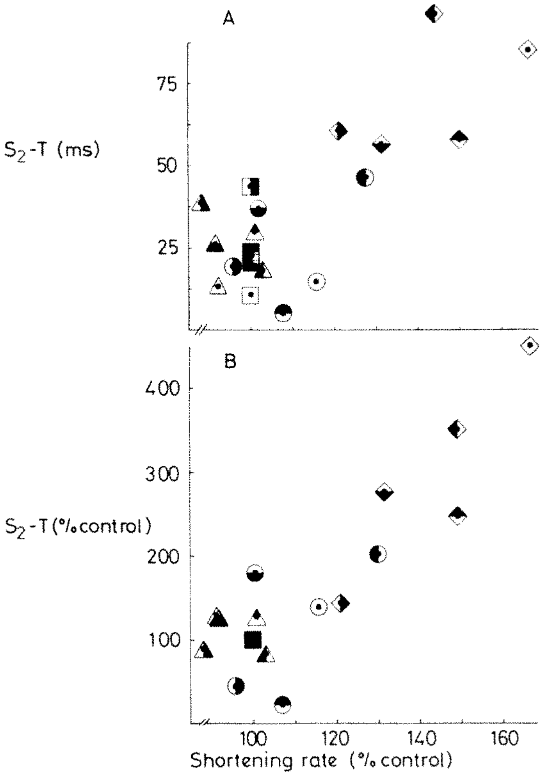

Fig. 3 *Effect of maximum shortening rate on S_2T interval: same key for intervention and subjects as in Fig. 2. Intervals plotted in* A *have been normalised to subjects' control values in* B.

Discussion

The findings that rapid myocardial shortening is associated with a longer QT interval and a shorter duration of mechanical systole are in keeping with studies in isolated muscle; but several other factors that might have contributed to these results should be considered. It is possible, for example, that the changes were the result of adrenergic stimulation during amyl nitrite. Catecholamines do shorten mechanical activation in isolated muscle,[5] and might, therefore, be expected to decrease the S_1S_2 interval; however, these agents do not lengthen the duration of the ventricular action potential,[6] making it unlikely that the increased S_2T interval after amyl nitrite was the result entirely of adrenergic influences. It should be mentioned that adrenergic stimulation has a variable influence on the QT interval in the intact animal.[7] Indeed, it is possible that the variability derives from the secondary effects of muscle shortening. Direct inotropic stimulation of the ventricle, either by rapid catecholamine infusion or by left stellate ganglion stimulation, which would be expected to cause a more rapid myocardial shortening, prolongs the QT interval. By contrast, slower infusion of catecholamines or more extensive stimulation, which might raise peripheral vascular resistance sufficiently to prevent the increased myocardial shortening, produces no increase, and sometimes a decrease of the QT interval.[7]

It is also possible that the changes in the S_2T interval were the result of the smaller end-systolic ventricular volumes after amyl nitrite. It is difficult to distinguish changes caused by active muscle shortening from those caused by short lengths. For example, the duration of mechanical activity in isolated muscle can be reduced substantially at short lengths,[8] but this effect is variable[5 8] and the reduction is very much diminished when the series compliance in the preparation is made stiffer, minimising internal shortening during "isometric" contractions (Ford, unpublished observations). This result together with the finding that action potential duration is not influenced by muscle length[9] suggest that the prolonged S_2T interval was not the result of a short end-systolic muscle length.

Although a prolonged QT or a shortened S_1S_2 interval have not previously been associated with rapid myocardial shortening, each has been described in coronary artery disease, where healthy myocardium might be expected to contract more rapidly, compensating for hypodynamic ventricular segments. For example, both changes have been described in acute myocardial infarction[10 11] and persistence of these changes has been correlated with a poor prognosis.[12 13] In addition, a prolonged QT interval has been correlated with a poor prognosis in chronic coronary artery disease[13] and this might reflect, in part, the correlation of a poor prognosis with the degree of ventricular hypokinesis that has been found directly in angiographic studies.[14]

It would be expected from studies in isolated muscle,[2 3] and isolated hearts,[15] that the relatively increased afterload imposed by cardiac failure would substantially increase the total duration of electromechanical systole (QS_2 interval). In fact, the reverse is usually found,[16 17] though there is substantial scatter in the results.[17] The shortening of total systole might also be explained by inhomogeneities in ventricular contraction, with the rapidly contracting segments relaxing earlier. Varying degrees of hypokinesis in the patients with heart failure could explain the larger standard deviation of the QS_2 measurement in this population.

References

1 Kaufmann RL, Hennekes R, Lab MJ. Demonstration of an "excitation-contraction recoupling" mechanism in mammalian ventricular myocardium. *Nature New Biology* 1971; **230:** 150–1.
2 Brady AJ. Onset of contractility in cardiac muscle. *J Physiol (Lond)* 1966; **184:** 560–80.
3 Brutsaert DL, De Clerck NM, Goethals MA, Housmans PR. Relaxation of ventricular cardiac muscle. *J Physiol (Lond)* 1978; **283:** 469–80.
4 DeMaria AN, Neumann A, Schubart PJ, Lee G, Mason DT. Systematic correlation of cardiac chamber size and ventricular performance determined with echocardiography and alterations in heart rate in normal persons. *Am J Cardiol* 1979; **43:** 1–9.
5 Sonnenblick EH. Force-velocity relations in mammalian heart muscle. *Am J Physiol* 1962; **202:** 931–9.
6 Nathan D, Beeler GW Jr. Electrophysiologic correlates of the inotropic effects of isoproterenol in canine myocardium. *J Mol Cell Cardiol* 1975; **7:** 1–15.
7 Abildskov JA. Adrenergic effects on the QT interval of the electrocardiogram. *Am Heart J* 1976; **92:** 210–6.
8 Allen DG, Jewell BR, Murray JW. The contribution of activation processes to the length-tension relation of cardiac muscle. *Nature* 1974; **248:** 606–7.
9 Dominguez G, Fozzard HA. Effect of stretch on conduction velocity and cable properties of cardiac Purkinje fibers. *Am J Physiol* 1979; **237:** C119–24.
10 Doroghazi RM, Childers R. Time related changes in the Q-T interval in acute myocardial infarction: possible relation to local hypocalcemia. *Am J Cardiol* 1978; **41:** 684–8.
11 Diamant B, Killip T. Indirect assessment of left ventricular performance in acute myocardial infarction. *Circulation* 1970; **42:** 579–92.
12 Heikkilä J, Luomanmäki K, Pyörälä K. Serial observations on left ventricular dysfunction in acute myocardial infarction: II Systolic time intervals in power failure. *Circulation* 1971; **44:** 343–54.
13 Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 1978; **57:** 1074–7.
14 Proudfit WL, Bruschke AVG, Sones FM Jr. Natural history of obstructive coronary artery disease: ten year study of 601 nonsurgical cases. *Prog Cardiovasc Dis* 1978; **21:** 53–78.
15 Patterson SW, Piper H, Starling EH. The regulation of the heart beat. *J Physiol (Lond)* 1914; **48:** 465–513.
16 Katz LN, Feil HS. Clinical observations on the dynamics of ventricular systole: 1. Auricular fibrillation. *Arch Intern Med* 1923; **32:** 672–92.
17 Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation* 1968; **37:** 149–59.

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QRS waveforms in right and left bundle-branch aberration*

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SUMMARY The electrocardiographic and vectorcardiographic features of right and left bundle-branch aberration were investigated in 32 patients during programmed electrical stimulation of the heart. Various types of aberration were seen, the right bundle-branch being affected to different degrees in 22 patients and the left in six; four patients developed right and left bundle-branch block at different times. Three of the patients who developed right bundle-branch block also showed loss of the first 40 ms anterior QRS forces, especially the second 20 ms; all also developed combined left and right ventricular conduction defects. Six other patients with right bundle-branch aberration, however, showed loss of QRS forces during the second 20 ms with preservation of the first 20 ms, in the absence of left ventricular conduction defects. Six patients showed anterior increases of the first 40 ms QRS forces, four also having additional left ventricular conduction defects.

The magnitude of the tangential velocity of inscription of the first 20 (and first 40) ms spatial QRS forces was unaffected by right bundle-branch aberration. In only four of the 26 patients with right bundle-branch aberration was less than 70 per cent of the QRS loop directed anteriorly. In all but one of these patients, however, the first 40 ms QRS forces were rotated in a counterclockwise direction even if the later forces inscribed a predominantly clockwise QRS loop in the horizontal plane.

Identification of the abnormalities produced by left and right aberrant conduction clarifies the positive features of ventricular arrhythmias. Furthermore, alteration of the first 40 ms QRS forces in right bundle-branch block will influence the ability to diagnose myocardial infarction accurately on the electrocardiogram.

Although right and left bundle-branch block are common there is little information about these disorders in patients without other cardiac abnormalities. While it is uncommon to record normal electrocardiograms before and after the development of bundle-branch block, whether occurring spontaneously[1 2] or during cardiac catheterisation,[3 4] it is only from the features seen in such patients that one can confirm the electrocardiographic criteria for bundle-branch block.

It is well established that left bundle-branch block affects the electrocardiographic diagnosis of both anterior and inferior infarction,[5] but the picture is less clear with right bundle-branch block.[6 7] Sandler and Marriott[8] have stressed the value of a monophasic R wave or an Rsr′ in V1 in ventricular arrhythmias, in contrast to an rSR′ in right bundle-branch aberration; these features may be the result of anterior direction of the QRS loop, sometimes with clockwise rotation. Since such a QRS loop has also been described in right bundle-branch block (type B)[4] it is important to establish how often such QRS loops are seen in right bundle-branch aberration as well as to seek characteristic features of the vectorcardiogram in this conduction defect. As there may be difficulty in the differentiation of ventricular arrhythmias from supraventricular arrhythmias complicated by left bundle-branch aberration we have also studied the latter defect.

Methods

Programmed stimulation of the heart was used to induce atrial and ventricular extrasystoles and rate dependent aberration as well as supraventricular tachycardia with aberration. Routine electro-

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physiological investigation was performed together with vectorcardiographic recordings in 43 patients to elucidate the nature of their arrhythmias. Three recording wires were inserted percutaneously through one or both femoral veins by the Seldinger technique and passed to the right side of the heart; one was positioned in the right atrium, one at the apex of the right ventricle, and one opposite the tricuspid valve, close to the bundle of His.[9] Orthogonal Frank lead electrocardiograms were recorded both with a Hewlett-Packard 1301B 3 channel electrocardiograph and an analogue magnetic tape recorder (Racal Thermionic Store 7). The tapes were played back through a PDP 12 laboratory computer and all complexes were displayed. Satisfactory complexes were selected and stored with cursor determination of the onset and offset. From these digital data the frontal and horizontal plane vectorcardiograms were printed out with a Complot DP1 digital XY plotter; the points were plotted at 4 ms intervals.[10] The magnitude of tangential velocity of QRS inscription was calculated between each 4 ms point in the frontal and horizontal planes and in three dimensions. Average figures for the first and second 20 ms have subsequently been described as the tangential QRS velocity. The computer also constructed scalar spatial electrocardiograms.

Because the terms complete and incomplete bundle-branch block have been criticised[11] we followed the classification of Witham[12] in which first degree bundle-branch block indicates a QRS duration of 120 ms or less, second degree a QRS duration between 120 ms and 150 ms, and third degree a QRS greater than 150 ms. The degree of right bundle-branch aberration in 13 patients with basal partial conduction defects was based on this classification. Witham has also suggested an alternative classification based on the normal QRS duration known for the patient concerned[12]: thus in first degree right bundle-branch block the QRS is prolonged by less than 30 ms in the affected complex, in second degree block additional QRS prolongation is between 30 and 50 ms. We have refined the accuracy of such measurements with our intracardiac recordings and have followed the second classification in the remaining 19 patients who initially had no conduction defects. Right and left bundle-branch blocks were diagnosed according to the criteria of Witham[12] and lesser left ventricular conduction defects often called hemiblocks were described according to established criteria.[4 13 14]

Results

Forty-three patients were studied of whom 32 developed aberration; 22 had right bundle-branch aberration (without left bundle-branch aberration), six left bundle-branch aberration (without right bundle-branch aberration), and four both right and left bundle-branch aberration at different times. Of the 32 patients, only one patient had a left ventricular conduction defect during sinus rhythm (pronounced left axis deviation) but 10 patients had incomplete right bundle-branch block of the basal QRS; one patient had old inferior infarction, and one had congestive cardiomyopathy with T wave changes in leads I and V3 to V6.

In nine, right bundle-branch aberration was induced by atrial extrastimuli, and atrial fibrillation occurred at the beginning of or during supraventricular tachycardia; in five this conduction defect was induced by atrial extrastimuli, supraventricular tachycardia, and atrial pacing; in the remaining 12 aberration only occurred after wire manipulation, atrial extrastimuli, or atrial pacing. The type of aberration seen was unrelated to the method of induction. Sixteen patients without any block of the basic QRS developed third degree right bundle aberration; lesser degrees were also seen at other times in 15 of these patients. The remaining 10 patients with right bundle-branch aberration included two with apparent complete right bundle-branch block of the basal QRS, but who developed increasing right bundle-branch aberration with atrial extrastimuli, as well as eight patients with varying grades of first and second degree right bundle-branch block.

The typical pattern of right bundle-branch aberration is shown in Fig. 1. The counterclockwise rotation of the initial 40 ms forces of the QRS was preserved in all but one patient. The most consistent feature of the lesser degrees of aberration was deviation of the terminal forces to the right and either anteriorly or slightly posteriorly; there was variable delay in the terminal forces which were more often superior than inferior. As the degree of right bundle-branch aberration increased so did the terminal delay which was always anterior; because midzone posterior forces were lost the QRS loop was predominantly anterior in the horizontal plane and the middle part of the loop tended to cross the efferent limb increasingly to the left and anteriorly (Fig. 2). Eventually the posterior forces were totally lost and the loop was anterior ($>90\%$) in all but five patients; in only four patients with third degree block was less than 70 per cent of the loop anterior and in only two of these patients was less than 50 per cent of the QRS loop anterior. In all patients the tangential velocities of inscription of the initial and second 20 ms QRS forces were the same as those of the normal QRS loop. Usually

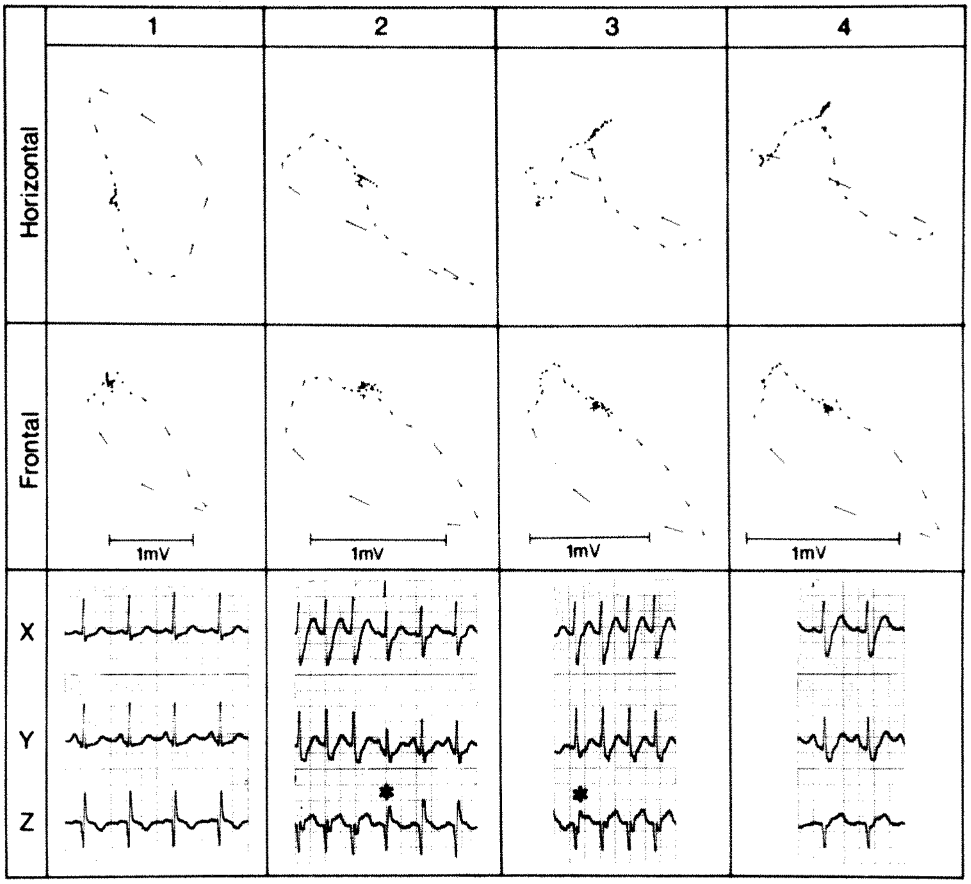

Fig. 1 *Horizontal and frontal plane vectorcardiograms (above) and orthogonal (Frank) electrocardiograms (below) of a patient developing right bundle-branch aberration.* Panel 1: *Sinus rhythm, normal conduction.* Panel 2: *The first sinus complex* after the end of supraventricular tachycardia shows first degree right bundle-branch aberration with loss of midzone posterior forces and development of terminal delay on the right.* Panel 3: *Second degree right bundle-branch aberration during supraventricular tachycardia (the complex shown is marked by an asterisk). QRS is now directed almost totally anteriorly, the terminal delay on the right being rotated anteriorly.* Panel 4: *Sinus rhythm with third degree right bundle-branch aberration produced by catheter pressure: note anterior QRS with increasing terminal delay.*

right bundle-branch aberration altered the direction of the frontal plane QRS complexes so that they became biphasic, and it was then impossible to determine the mean QRS accurately (Fig. 2). Usually the first 60 ms QRS forces were directed more superiorly and to the left than the normal complexes. In three patients, however, these forces were directed more inferiorly. These complexes may have shown right axis deviation because of an associated conduction defect, an isolated finding also seen in two of these patients.

Alteration of the initial forces of the QRS could occur with right bundle-branch aberration. Thus in five patients increase of either the first or second 20 ms anterior forces occurred with the lesser degrees of right bundle-branch aberration (Fig. 3, panel 2; Fig. 4, panel 2). With increasing right bundle-branch aberration this increase of the first 20 ms anterior QRS forces was less obvious (Fig. 3 and 4, panel 3). In one patient, despite the return of normal initial anterior QRS forces with second degree right bundle-branch aberration, the QRS loop remained predominantly anterior and was unusual in that the crossover was eliminated (Fig. 4). It was followed by the development of a form of bundle-branch block not seen previously (Fig. 4,

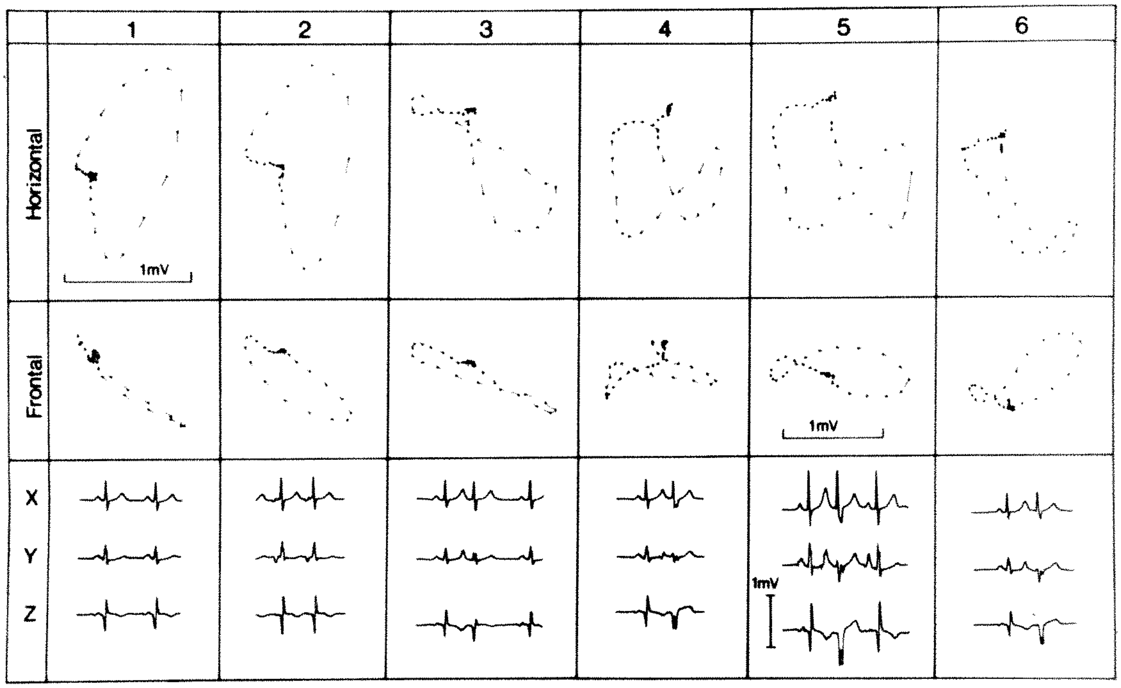

Fig. 2 *Horizontal and frontal plane vectorcardiograms (above) and orthogonal (Frank) electrocardiograms (below) of a patient developing right bundle-branch aberration.* Panel 1: *Sinus rhythm, normal conduction.* Panel 2: *First degree right bundle-branch aberration. The terminal forces to the right are increased and are directed slightly superiorly: the first 40 ms anterior QRS forces are also increased.* Panel 3: *A premature atrial stimulus produces second degree right bundle-branch aberration. The loop is predominantly anterior because of loss of midzone posterior QRS forces; terminal forces are increased to the right and the QRS is biphasic in both planes.* Panel 4: *Third degree right bundle-branch aberration produced by a more premature atrial stimulus. The QRS is now almost totally anterior and biphasic. The crossover point has moved to the left; in the frontal plane the first part of the QRS is further left and the second part clearly directed to the right.* Panel 5: *A premature atrial stimulus produces third degree right bundle-branch aberration. There is multiformity of right bundle-branch aberration, that is this complex is of a different shape as compared with that shown in Panel 4.* Panel 6: *Second degree right bundle-branch aberration is associated with left axis deviation. The QRS is still biphasic in both planes, but less of the QRS is directed to the right. The QRS is almost totally anterior and the crossover point to the left, with less overlap than in right bundle-branch aberration alone.*

panel 5), but which was also encountered in one patient in association with third degree right bundle-branch aberration alone. In both patients the tangential velocity of the initial anterior and subsequent posterior QRS forces was slower than normal; in the frontal plane QRS inscription was as slow as is seen in left bundle-branch block and the QRS loop was directed inferiorly and to the right. In the horizontal plane the loop was also directed posteriorly, with terminal delay to the right and slightly anteriorly as in right bundle-branch block. The QRS pattern in lead X or V6 was not obviously different from that in right bundle-branch block. Alteration of initial tangential QRS velocity was probably the result of an additional significant left ventricular conduction defect.

Loss of initial anterior QRS forces was also common in association with third degree right bundle-branch block. It occurred after the first 20 ms forces in six patients and included the first 30 ms in three patients, leading to loss of initial counterclockwise inscription in the horizontal plane; the loop almost became clockwise but was only totally clockwise in one patient. There was an association between abbreviation of anterior QRS forces and at least transient left ventricular conduction defects.

Left bundle-branch aberration was initiated by extrastimuli in four patients and supraventricular tachycardia in six. Left bundle-branch aberration

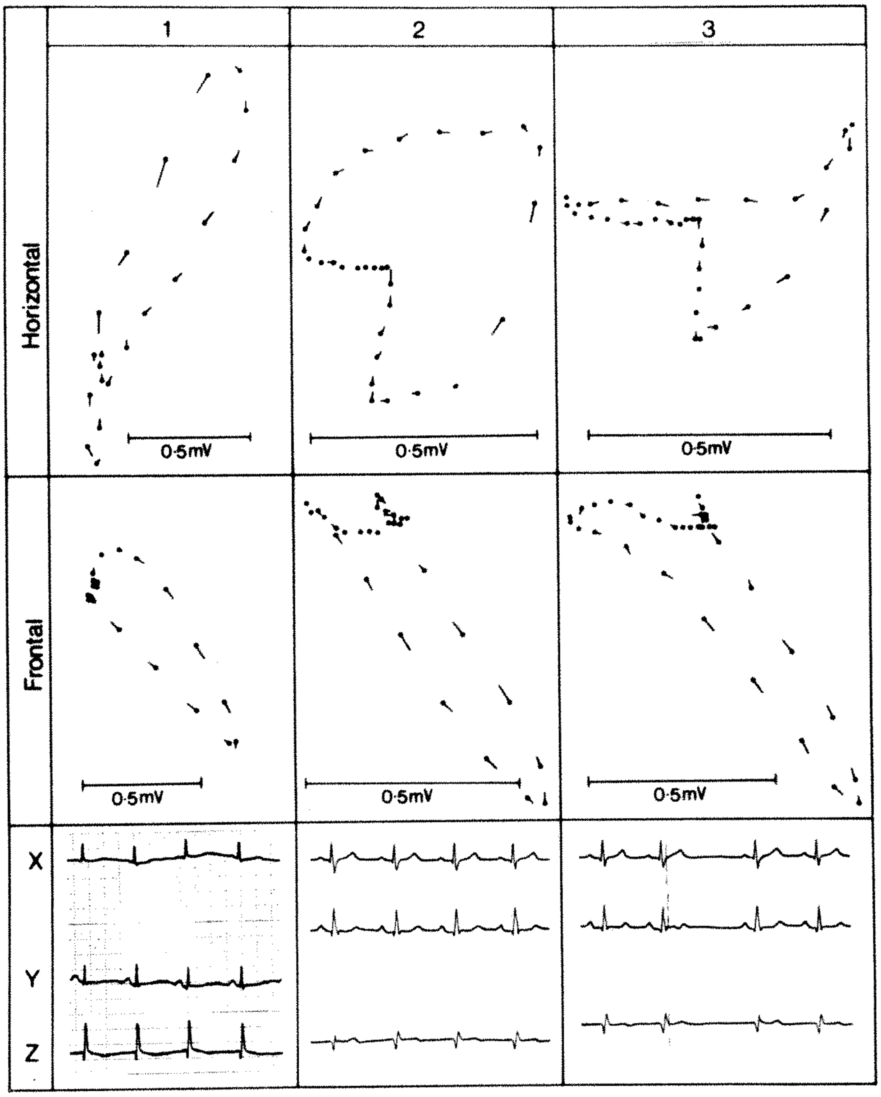

Fig. 3 *Horizontal and frontal plane vectorcardiograms (above) and orthogonal (Frank) electrocardiograms (below) of a patient with right bundle-branch aberration.* Panel 1: *Sinus rhythm, normal conduction.* Panel 2: *First degree right bundle-branch aberration produced by catheter manipulation causes decreased midzone posterior QRS forces and slight increase of the second 20 ms anterior QRS forces.* Panel 3: *The sinus beat, following a pause after premature atrial stimulation, produced second degree right bundle-branch aberration with prominent terminal forces directed to the right. There is loss of posterior forces and reduction of the second 20 ms anterior forces.*

was associated with loss of anterior forces in the horizontal plane (Fig. 3). In seven patients this affected the first 20 ms, six showing total loss of anterior forces; in three the loss of anterior forces was confined to the later part of the QRS and the direction of the initial 20 ms forces was unaffected. In all patients the frontal plane loop was small and the velocity of inscription was very slow. The initial forces in these seven patients were directed more superiorly, as was the R point. Left axis deviation with left bundle-branch block, however, was only produced in six patients. Tangential velocity of inscription of both the first and second 20 ms QRS forces was reduced, but the tangential velocity of

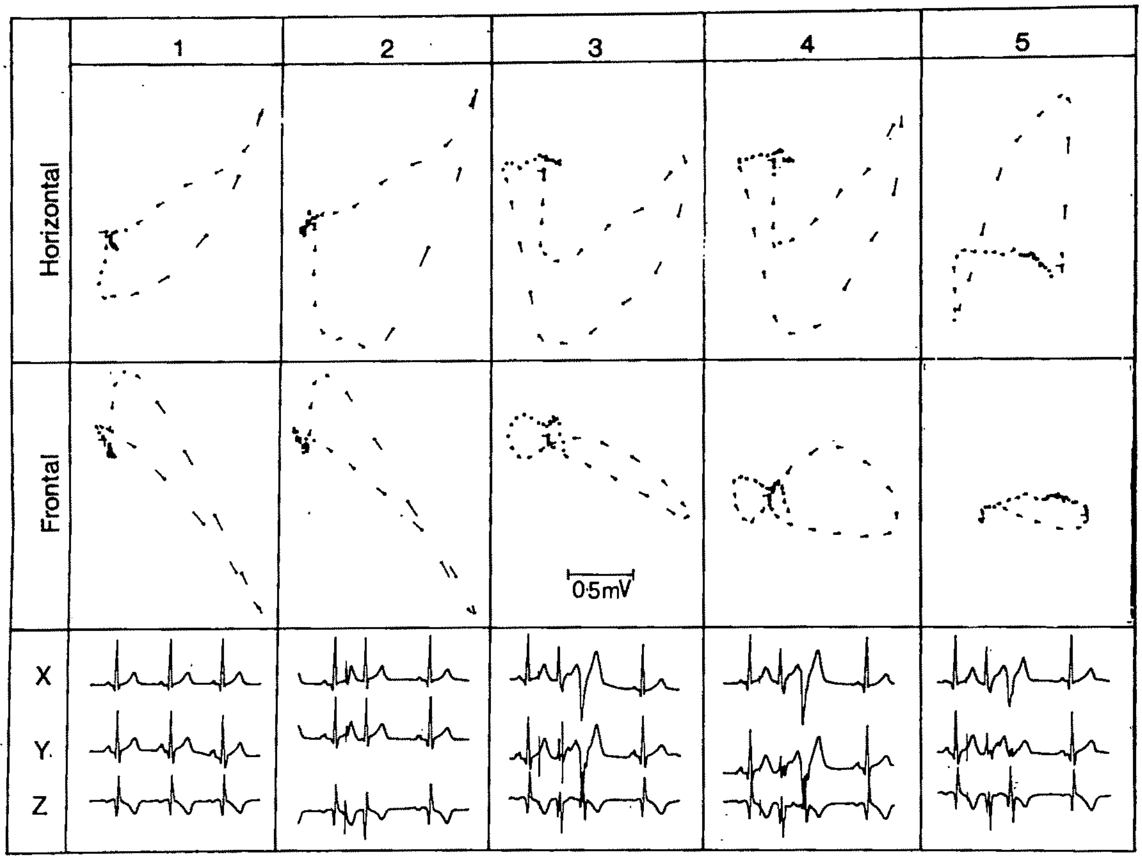

Fig. 4 *Horizontal and frontal plane vectorcardiograms (above) and orthogonal electrocardiograms (below) of a patient with right bundle-branch aberration.* Panel 1: *Sinus rhythm, normal conduction.* Panel 2: *A premature atrial stimulus produced increased anterior QRS forces without loss of posterior forces.* Panel 3: *The first QRS complex after two consecutive atrial extrastimuli shows second degree right bundle-branch aberration. The midzone posterior QRS forces are reduced. The whole loop is swung anteriorly, but initially still remains counterclockwise. The prominent initial anterior forces have decreased. In the frontal plane the loop is obviously biphasic with some orientation of the first part to the left.* Panel 4: *Additional left axis deviation with right bundle-branch aberration of the first premature impulse.* Panel 5: *The second premature impulse shows extreme right axis deviation. Initial anterior forces are abbreviated and the loop lies on the left posterior quadrant; the terminal QRS is directed to the right and anteriorly.*

the later forces, which are directed posteriorly, was always more than 10 mV/s in the horizontal plane. The QRS duration was 140 ms or more in all patients with left bundle-branch aberration, but in two patients there were similar QRS configurations albeit with a duration of 120 ms or less. Two patients also showed left axis deviation with other atrial extrastimuli. Seven patients had left bundle-branch aberration during tachycardia, but only one of these had such aberration with atrial extrastimuli, though two others had right bundle-branch aberration with atrial extrastimuli (Fig. 5).

Discussion

This study has clarified the QRS waveform of right and left bundle-branch block in patients investigated because of arrhythmias; there were only two patients with primary cardiac disease. Earlier studies have been based either on postoperative bundle-branch block or have included a large proportion of patients with cardiac disease.[4] These authors described the vectorcardiographic features of aberrant conduction produced by premature atrial stimulation. Vectorcardiograms provide in-

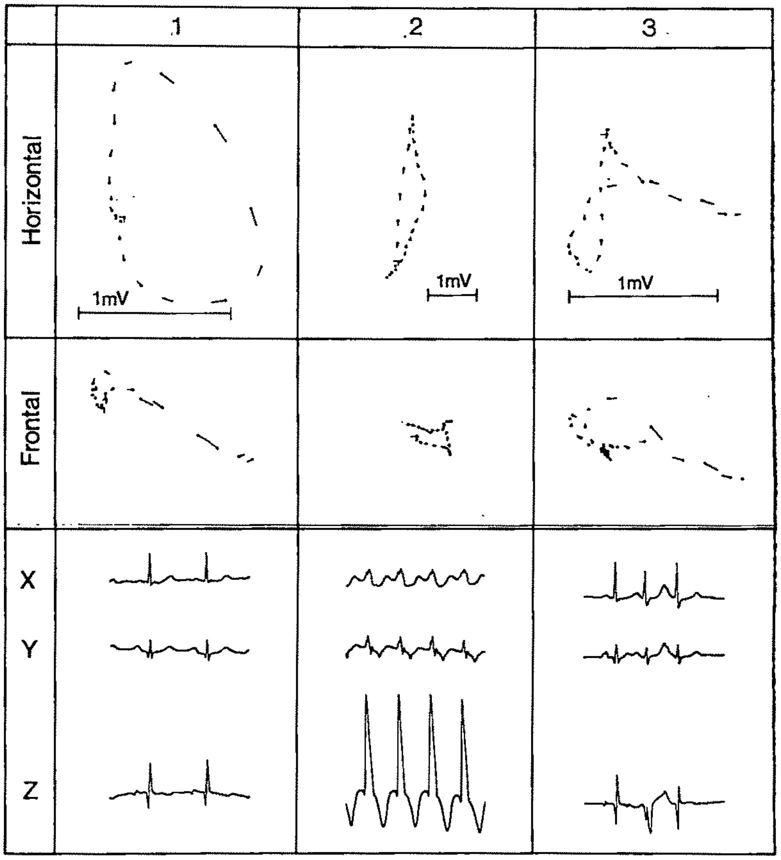

Fig. 5 *Horizontal and frontal plane vectorcardiograms (above) and orthogonal electrocardiograms (below) of a patient developing both right and left bundle-branch aberration.* Panel 1: *Sinus rhythm showing QRS changes of old inferior infarction.* Panel 2: *Left bundle-branch block develops during supraventricular tachycardia.* Panel 3: *A premature atrial stimulus produces third degree right bundle-branch block with preservation of initial counter-clockwise rotation in the horizontal plane despite a totally anterior QRS loop.*

formation on ventricular excitation in all three planes, which is difficult to achieve by multiple electrocardiographic leads during programmed electrical stimulation or severe arrhythmias. Our study was based on vectorcardiograms and we included examples of aberration complicating supraventricular arrhythmias, atrial pacing, and induced atrial extrasystoles. We have identified important differences between aberration and ventricular arrhythmias.

The QRS waveform of pure, isolated third degree right bundle-branch block is easily explained.[12 15] The right septal surface is excited 30 to 40 ms later than normal and right ventricular activity persists for 20 ms longer than normal so that the QRS duration is increased by 50 to 60 ms. Normally the sequence of depolarisation of the right ventricle is the apex, then the lateral wall, and finally the infundibulum. Thus in first degree right bundle-branch block only infundibular activation will be shown after the end of left ventricular excitation and the terminal QRS forces will be directed superiorly to the right and either just posteriorly or just anteriorly; if conduction through the anterolateral wall is also sufficiently delayed, the terminal forces will be increased to the right and anteriorly. If activation of the right ventricular apex is also delayed the QRS forces will be directed even more anteriorly, but delay will be no more pronounced on the right, since the crossover point is moved to the left.

Septal activation normally takes 10 to 20 ms and proceeds from left to right and anteriorly so that the first 20 ms QRS forces are not affected by right bundle-branch block.[12] However, thereafter alteration of QRS forces may be caused by delayed septal depolarisation and/or prolonged right ventricular activation. Such changes could be expected in lesser degrees of right bundle-branch block, and increased anterior forces at this time may occur if such forces are not as effectively cancelled as with normal ventricular excitation. With an increasing degree of right bundle-branch block these septal and right ventricular forces will occur later, when normal left ventricular depolarisation has directed the QRS more posteriorly, so that cancellation can occur. This concept is supported by the loss of posterior forces from the left ventricle in right bundle-branch aberration. Alterations of septal depolarisation produced by conduction defects and anatomical variations affecting the bundle-branch system might increase this tendency, and the electrical position of the heart in relation to the fifth intercostal space both before and after development of right bundle-branch block is also important.

With the development of right bundle-branch block the QRS loop usually becomes biphasic in the frontal plane with increased leftward forces for the first 60 ms, presumably because of loss of early rightward forces from the right ventricle. There may also be loss of anterior forces after the first 20 ms for the same reason but coincidental left ventricular conduction defects may account for this change. Because of the variable anatomy of the left ventricular conducting system[16] one must expect many different combinations with right bundle-branch aberration producing differences in the morphology of the QRS complexes.

We were unable to divide right bundle-branch aberration into types with an anterior clockwise loop (type B) and a posterior counterclockwise loop (type A).[13] Intermediate types were common and have been recorded before, but different authors have either classified type B as a predominantly clockwise loop whatever the direction of the initial 40 ms or have not clearly stated whether all the loop must be clockwise.[4 14] Totally anterior QRS loops appear to be most frequent in third degree right bundle-branch block though the counterclockwise rotation of the first 40 ms QRS forces is preserved. Transition to a totally clockwise loop only requires slight loss of anterior and rightwards forces and alteration in the superior and inferior position of the loop so that the crossover is eliminated. Since left axis deviation may reduce anterior forces directing initial forces less to the right, a totally clockwise loop may be more frequent when left axis deviation is associated with an anterior right bundle-branch block loop. Obviously other factors such as a small anterior infarct or left septal fibrosis could have the same effect. Our findings and those of Kulbertus *et al.*[4] contradict the suggestion that an anterior QRS loop in right bundle-branch block is more frequent when there is also left ventricular disease.[13] Not only do anterior right bundle-branch block loops not indicate right ventricular hypertrophy, but the midzone and later anterior forces negate posterior left ventricular forces and therefore mask electrocardiographic signs of left ventricular hypertrophy.[5]

The more posterior QRS loop often found in right bundle-branch block may result from associated left ventricular hypertrophy or alterations of electrical position with age, as the QRS loop is often more anterior below the age of 40 years than in older subjects.

The preservation of the normal direction of the initial 20 ms QRS forces in right bundle-branch aberration has important implications. Alterations of the second 20 ms QRS forces anteriorly or posteriorly are also important, however, since anterior infarction may affect either the first or second 20 ms QRS forces or both.[5] It is therefore obvious that loss of the first 20 ms anterior forces still permits the diagnosis of anterior infarction in the presence of isolated right bundle-branch block; later loss of anterior forces interferes, however, with diagnosis. Anterior infarction may be concealed by increase of initial anterior forces, in keeping with our previous results[5] and those of Goldman and Pipberger.[7]

The QRS waveform in left bundle-branch block was distinctive. There was diminution and sometimes total loss of initial anterior forces, initial forces being directed variably, presumably depending on the course of activation from the right. After the slow initial forces the main efferent limb of the QRS is directed posteriorly and is inscribed more quickly. The apex of the loop is inscribed more slowly but the end of the loop may be faster, perhaps because of excitation of His-Purkinje fibres. Though it is known that the QRS in left bundle-branch block is usually 10 to 20 ms longer than that of right bundle-branch block, we have seen QRS durations considerably less than 150 ms, particularly in supraventricular tachycardia complicated by aberration. Though incomplete left bundle-branch block could be defined in those who at other times showed complete left bundle-branch aberration, in some patterns of left axis deviation or loss of right anteroseptal forces, one may see loss or diminution of Q waves in left-sided leads and lead Z (diminution of initial r wave in V1 and V2). We do not consider such changes diagnostic of incomplete left bundle-branch block alone.

The variety of minor changes of electrical axis in the frontal or horizontal plane could also be ascribed to left ventricular conduction defects caused by the variable anatomy of the left-sided conducting system[16] but slight changes may only reflect alterations of anatomical position produced by variation in the duration of diastole. *We obtained no evidence for or against a distinct left ventricular conduction defect producing prominent anterior forces.* Prominent anterior QRS forces occur for several reasons, among which incomplete and complete right bundle-branch block are important.

The first 20 ms QRS forces probably comprise normal left-to-right septal activation and the second 20 ms QRS forces are predominantly caused by normal left ventricular activation.[12] In left bundle-branch aberration tangential QRS velocity is reduced, especially in the frontal plane. In the horizontal plane there is initial delay of 20 ms or less before acceleration into the efferent limb of the QRS. In left bundle-branch block we have not seen an average tangential velocity of the QRS inscription in the horizontal plane of less than 10 mV/s affecting either the second 20 ms or total first 40 ms QRS forces. The direction of the QRS forces and the tangential velocity of inscription of the QRS are important differentiating features between aberrant conduction and ventricular arrhythmias.

Our studies of ventricular arrhythmias[10] showed the following features that have not been observed in either right or left bundle-branch block: (1) a QRS loop totally directed into the left anterior quandrant; (2) more than 50 per cent of a left-sided QRS loop directed into the left anterior quadrant; (3) total anterior QRS loop with counterclockwise rotation (one cause of "Rr" or "R" patterns in V1); (4) slow inscription of the QRS loop, lasting more than 20 ms; (5) tangential velocity of inscription of any part of the first 40 ms of any spatial QRS loop resembling right bundle-branch block of less than 10 mV/s; (6) tangential QRS velocity in the horizontal plane less than 10 mV/s between the 20 and 40 ms vector points in examples of "left bundle-branch block complexes".

Right bundle-branch aberration is characterised by a biphasic QRS, particularly in the horizontal plane. Thus notching of the QRS in V1 and V2 or lead Z is diagnostic; lesser changes may be deceptive and a deep S wave in V5 or V6 is not diagnostic. Total clockwise anterior loops in the horizontal plane, that is loss of the initial counterclockwise loop, occur in ventricular arrhythmias and appear to be rare in right bundle aberration alone. These loops also produce R waves in V1, which are usually monophasic but may show a notch or a slur on the upstroke. This feature and the accuracy of lesser abnormalities of tangential QRS velocity become more accurate if the normal QRS contour is known. There are other less significant features of ventricular arrhythmias: inferior or rightward orientation of ventricular extrasystoles is common[10] but this is infrequent in uncomplicated right and left bundle-branch aberration; increased maximum spatial QRS voltage so that large QRS complexes are found in both frontal and horizontal planes; monophasic QRS loops are suggestive of ventricular arrhythmias unless they are directed into the left posterior quadrant as may occur with left bundle-branch block aberration.

We must, however, stress that while most ventricular arrhythmias can be distinguished from supraventricular arrhythmias with aberrant conduction, this is not always possible; in particular, ventricular arrhythmias may be indistinguishable from atrial fibrillation in the Wolff-Parkinson-White syndrome.

References

1 Scherlis L, Lee YC. Transient right bundle branch block: an electrocardiographic and vectorcardiographic study. *Am J Cardiol* 1963; **11**: 173–86.
2 Krikler DM, Lefevre D. Intermittent left bundle-branch block without obvious heart-disease. *Lancet* 1970; **i**: 498–500.
3 Peñaloza D, Gamboa R, Sime F. Experimental right bundle branch block in the normal human heart. *Am J Cardiol* 1961; **8**: 767–79.
4 Kulbertus HE, De Leval-Rutten F, Casters P. Vectorcardiographic study of aberrant conduction. *Br Heart J* 1976; **38**: 549–57.
5 Talbot S, Dreifus LS, Watanabe Y, Chiang R, Morris K, Reich M. Diagnostic criteria for computer-aided electrocardiographic 15 lead system. Evaluation using 12 leads and Frank orthogonal leads with vector display. *Br Heart J* 1976; **38**: 1247–61.
6 Cohen SI, Lau SH, Stein E, Young MW, Damato AN. Variations of aberrant ventricular conduction in man: evidence of isolated and combined block within the specialised conduction system. An electrocardiographic and vectorcardiographic study. *Circulation* 1968; **38**: 899–916.
7 Goldman MJ, Pipberger HV. Analysis of the orthogonal electrocardiogram and vectorcardiogram in ventricular conduction defects with and without myocardial infarction. *Circulation* 1969; **39**: 243–50.
8 Sandler IA, Marriott HJL. The differential morphology of anomalous ventricular complexes of RBBB-type in lead V_1: ventricular ectopy versus aberration. *Circulation* 1965; **31**: 551–6.
9 Curry PVL. Fundamentals of arrhythmias: modern methods of investigation. In: Krikler DM, Goodwin JF, eds. *Cardiac arrhythmias: the modern electrophysiological approach.* London: WB Saunders, 1975: 39–80.
10 Talbot S, Kilpatrick D, Weeks B. Vectorcardiographic features of ventricular extrasystoles correlated with conventional scalar electrocardiographic interpretation. *Br Heart J* 1978; **40**: 883–90.
11 Wu D, Denes P, Dhingra R, Rosen KM. Bundle branch block. Demonstration of the incomplete nature of some "complete" bundle branch and fascicular blocks by the extrastimulus technique. *Am J Cardiol* 1974; **33**: 583–9.
12 Witham AC. *A system of vectorcardiographic interpretation.* Chicago: Year Book Medical Publishers, 1975: 22–84.

13 Saltzman P, Linn H, Pick A. Right bundle-branch block with left axis deviation. *Br Heart J* 1966; **28:** 703–8.
14 Kulbertus H, Collingnon P, Humblet L. Vectorcardiographic study of the QRS loop in patients with left anterior focal block. *Am Heart J* 1970; **79:** 293–303.
15 Durrer D, Janse MJ, Lie KI, van Capelle FJL. Human cardiac electrophysiology. In: Dickinson CJ, Marks J, eds. *Developments in cardiovascular medicine*. Lancaster: MTP Press, 1978: 53–75.
16 Kulbertus HE. Concept of left hemiblocks revisited: a histopathological and experimental study. *Adv Cardiol* 1975; **14:** 126–35.

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High-fidelity, infinite time constant calibrated pressure apexcardiogram and its correlation with high-fidelity left ventricular pressure*†

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SUMMARY A technique of recording the pressure apexcardiogram by means of a high-fidelity piezoresistive transducer has been developed in our laboratory. It permits the quantification of pressure with which the transducer is applied to the chest wall as well as the pressure changes during a cardiac cycle. In this preliminary report, apexcardiographic pressures were compared with simultaneously recorded high-fidelity left ventricular pressure in 32 patients. There were no significant differences in the timing of the left ventricular systolic upstroke and the "O" point. Peak dP/dt of the apexcardiogram occurred (10±13 ms) significantly earlier than the intraventricular pressure recordings. Though there was a correlation between developed diastolic pressure (end-diastolic minus early diastolic pressure) measured by the apexcardiogram (20±14 mmHg) and intraventricular pressure recordings (11±6 mmHg), the former was significantly higher. Pressure overshoots in early and late diastole contributed to this overestimation by the apexcardiogram but the relative contribution of each phase varied from patient to patient. There was a similar correlation between systolic pressures, but this index tended to be underestimated by the apexcardiogram.

The data suggest that the apical impulse is not solely caused by the passive transmission of left ventricular pressure. The convenient, direct method of measuring application and developed pressure at the apex described in this report permits scientific investigation of the forces responsible for genesis of this impulse and its alteration in pathological states.

Conventional apexcardiography provides a record of relative displacement, that is, displacement of the chest wall enclosed by the transducer pick-up cup in relation to the surrounding area at the rim of the cup.[1 2] The impulse cardiography of Mounsey[3] and kinetocardiography of Eddleman[4] record absolute chest wall movement at the point of measurement in relation to a fixed point in space. Both relative and absolute displacement recordings are significantly modified by physical properties of the chest wall and the application or loading pressure. Therefore, it has been felt for some time that the measurement of the force or pressure which causes the displacement would be more meaningful and reliable. The basic principles underlying this technique have been elucidated by Willems *et al.*[5] using either fluid-filled pressure transducers or Telco catheters in dogs and fluid-filled pressure transducers in man. Gleichmann *et al.*,[6] and Witte and Heublen[7] used strain-gauge transducers in human subjects to measure the force on the chest wall at the point of apical impulse, but, unfortunately, their technique did not permit measurement of application pressure, which must be known to calibrate the system properly.

We have developed a technique of recording the apexcardiogram by means of a high-fidelity piezoresistive pressure transducer. It permits quantification of both application pressure as well as pressure changes during the cardiac cycle. In this preliminary report, we compare the results of external pressure recordings with intraventricular pressure recordings obtained by a similar transducer.

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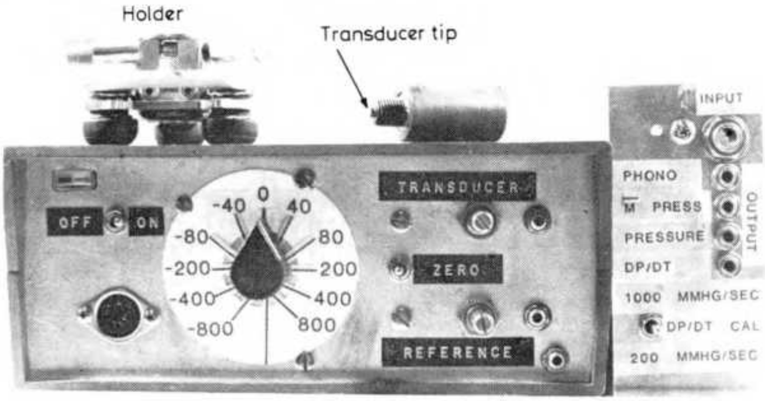

Fig. 1 *Prototype of pressure apexcardiographic system used in this study. The positive numbers on the amplifier are used to calibrate the pressure signal while the negative numbers on the left-hand side indicate the negative pressure applied to offset the loading pressure.*

Subjects and methods

Our apexcardiographic transducer (Fig. 1) is a piezo-resistive strain gauge mounted on a thin stainless steel diaphragm approximately 2 mm in diameter. The dynamic range of the transducer is from zero to 1520 mmHg with a flat frequency response from zero to 10 000 Hz.

The four-leg active bridge is supplied with a highly regulated direct current voltage of ±3 volts. The signal voltage is amplified by an instrumentation amplifier so that an output of 1 volt is equivalent to a pressure of 100 mmHg. The system is calibrated with air pressure using a sphygmomanometer.

The voltage generated by the total pressure (which is the sum of static pressure and dynamic pressure) is fed into the summing junction of an operational amplifier. A negative voltage is then applied to offset the output so that the "0" point of the apexcardiogram is close to the baseline. The loading pressure is determined from the negative voltage applied since the latter is calibrated (1 volt = 100 mmHg). The negative voltage opposing the loading pressure could be applied in steps of 0, 40, 80, 200, 400, and 800 mmHg. The signal is then passed through a low-pass Butterworth filter with 40 db/decade roll-off above 25 Hz and electronically differentiated and calibrated (1 volt = 1000 mmHg/s) to measure dP/dt of the apexcardiogram. The undifferentiated signal is used to record the apexcardiographic pressure.

With the patient in the semi-left lateral recumbent position, the apexcardiograph transducer was held to the chest wall at the point of maximal apical impulse by means of a three-legged holder fastened to the patient with a three-way elastic strap. The transducer was advanced in the centre of the holder by means of a screw; thus, the loading pressure could be controlled by adjusting the advancement of the transducer. The apexcardiogram was recorded with a loading pressure of 200 and 400 mmHg. Loading pressure was increased beyond 200 mmHg until the maximal amplitude of the systolic wave was obtained. Respiration was held at the point where maximal amplitude was achieved.

Simultaneous recordings of the apexcardiogram, left ventricular pressure, and their first derivatives were recorded in 32 patients (23 men, nine women) undergoing cardiac catheterisation. Their mean age

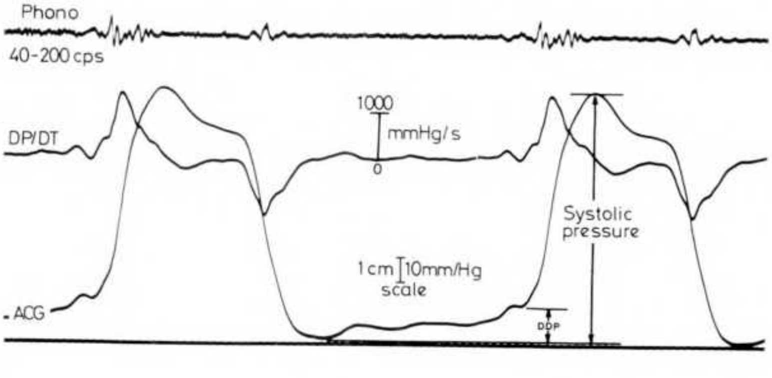

Fig. 2 *Calculation of pressures from the apexcardiogram (ACG). The signal has also been processed to yield the first derivative of pressure (dP/dt) and a phonocardiogram (phono). Developed diastolic pressure (DDP) is measured from the early diastolic nadir to the onset of the systolic wave upstroke. Systolic pressure is measured from the early diastolic nadir to the peak of the systolic wave.*

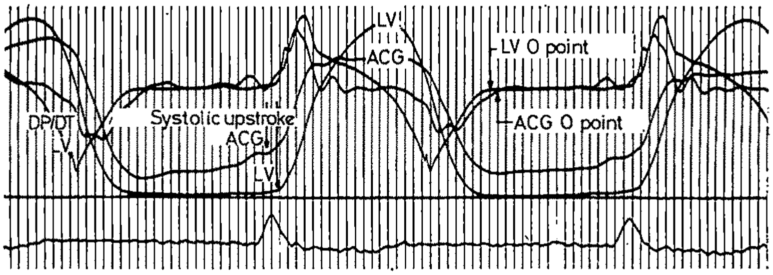

Fig. 3 *Identification of the onsets of the systolic wave upstroke and "0" points in simultaneous recordings of ACG and left ventricular (LV) pressure and their first derivatives (dP/dt). Systolic upstroke onsets were directly identified in the pressure traces. The "0" point was the point where a dP/dt of zero mmHg/s was reached in early diastole.*

was 52 ± 14 years (±SD). Their diagnoses were: atherosclerotic heart disease in 12, valvular aortic stenosis in six, aortic regurgitation in seven, mitral regurgitation in four, cardiomyopathy in two, and coarctation of the aorta in one. Three patients were in atrial fibrillation, and the remainder were in sinus rhythm. Left ventricular pressure was recorded with a Millar micromanometer catheter. Micromanometer pressure was corrected for the effect of gravity by superimposing its pressure over the fluid-filled pressure during slow rates of pressure change in diastole. The zero reference level for pressure measurement was 5 cm below the sternal angle.

For each patient, the following measurements represented an average of five consecutive cardiac cycles and were obtained from recordings taken at a paper speed of 100 to 200 mm/s, with 20 ms time lines. Developed diastolic pressure of the apexcardiograph was measured from the "0" point to the onset of the systolic wave upstroke (Fig. 2). Left ventricular developed diastolic pressure was left ventricular end-diastolic pressure minus minimum left ventricular early diastolic pressure. Since the left ventricular early diastolic nadir was not a temporally distinct point in most patients, zero dP/dt in early diastole was selected as the "0" point for both the left ventricle and apexcardiogram in all cases (Fig. 3 and 4). Systolic pressure of the apexcardiogram was measured from the "0" point to the peak of the systolic wave (Fig. 2); apexcardiograph systolic pressure was not measured in seven patients since recordings were obtained only at high gain in these subjects.

Left ventricular and apexcardiograph pressure recordings were compared with respect to the occurrence of the onset of the systolic upstroke, "0" point and peak dP/dt. The following comparisons of pressures were made: left ventricular end-diastolic pressure versus left ventricular developed diastolic pressure; left ventricular end-diastolic pressure versus apexcardiograph developed diastolic pressure; left ventricular developed diastolic pressure versus apexcardiograph developed diastolic pressure; left ventricular systolic pressure versus apexcardiograph systolic pressure; left ventricular

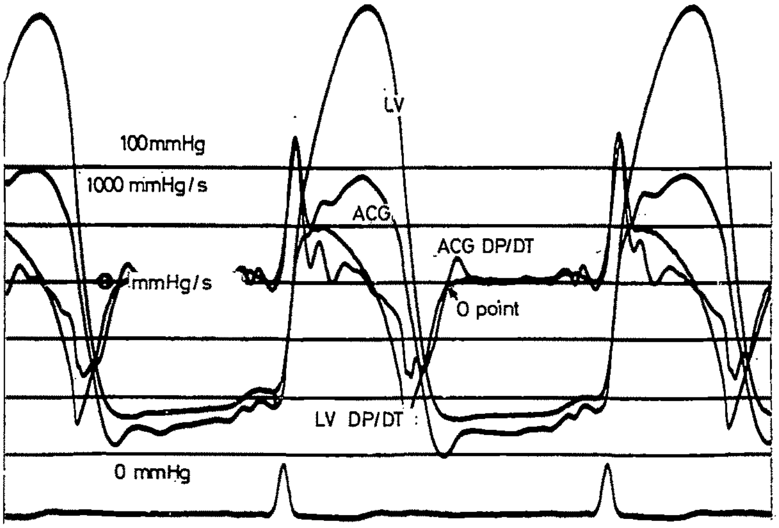

Fig. 4 *Simultaneous left ventricular and ACG pressure and dP/dt. The onsets of the systolic upstroke and "0" points are simultaneous. Developed diastolic pressure of the ACG is greater than LV developed diastolic pressure. ACG systolic pressure is less than the LV systolic pressure, but peak dP/dt's are identical.*

peak dP/dt versus apexcardiograph peak dP/dt. The comparison was made using paired data and Student's t test. The null hypothesis tested statistically was no significant difference between pairs. For these data, Pearson's correlation coefficient was derived and regression analysis performed assuming a linear relation. Only correlation coefficients significantly different from zero are reported.

Results

ONSET OF LEFT VENTRICULAR SYSTOLIC WAVE

The onsets of the systolic waves in the apexcardiogram and left ventricular pressure traces were not significantly different. They were simultaneous in 24 of the 32 patients (Fig. 4), occurred 10 to 40 ms earlier in the apexcardiogram of six patients (Fig. 3), and were earlier by 20 ms in the left ventricular pressure traces of two patients.

"0" POINT

The "0" point of the apexcardiogram was simultaneous with left ventricular pressure in 22 patients (Fig. 4), preceded it by 10 to 40 ms in eight patients, and followed it by 20 and 40 ms, respectively, in two patients (Fig. 3). The mean difference (±SD) was 5 (±16) ms which was not statistically significant.

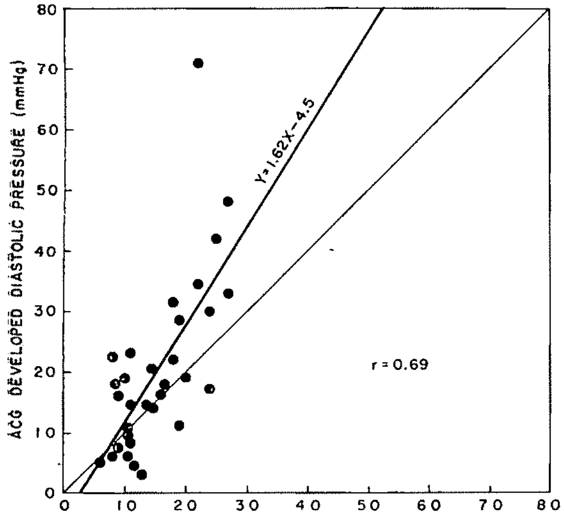

Fig. 5 *Left ventricular end-diastolic pressure versus developed diastolic pressure determined from the apexcardiogram. The heavy solid line is the regression line, and the light solid line is the line of identity.*

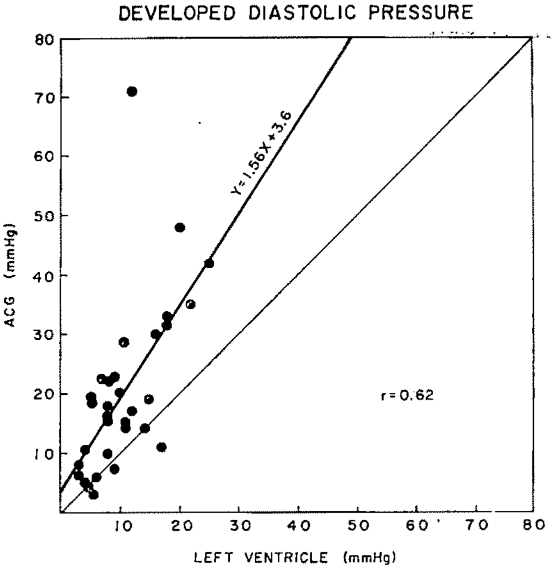

Fig. 6 *Left ventricular developed diastolic pressure versus apexcardiogram developed diastolic pressure. The heavy solid line is the regression line and the light solid line is the line of identity.*

OCCURRENCE OF PEAK DP/DT

Peak dP/dt of the apexcardiogram preceded that of left ventricular pressure by 5 to 35 ms in 20 patients (Fig. 3), occurred simultaneously with it in nine patients (Fig. 4), and followed it by 5 to 15 ms in three patients (mean (±SD), 10 (±13) ms; $p < 0{\cdot}001$).

DIASTOLIC PRESSURE

Left ventricular end-diastolic pressure in the 32 patients ranged from 6 to 27 mmHg (mean ±SD = 15 ±6 mmHg). Developed diastolic left ventricular pressure ranged from 3 to 22 mmHg (mean ±SD = 11 ±6 mmHg) and though this correlated with left ventricular end-diastolic pressure ($r = 0{\cdot}79$), the two were significantly different ($p < 0{\cdot}001$). The developed diastolic pressure of the apexcardiogram ranged from 3 to 71 mmHg (mean ±SD = 20 ±14 mmHg) and correlated with left ventricular end-diastolic pressure ($r = 0{\cdot}69$) (Fig. 5) and left ventricular developed diastolic pressure ($r = 0{\cdot}62$) (Fig. 6), but was systematically higher than both ($p < 0{\cdot}025$ and $p < 0{\cdot}001$, respectively.)

Left ventricular and apexcardiographic pressure contours could be superimposed during mid-diastolic slow rates of pressure change in 22 patients (Fig. 7). In 16 of these 22, the developed diastolic pressure of the apexcardiogram exceeded that of the left ventricle by 1 to 18 mmHg (mean ±SD =

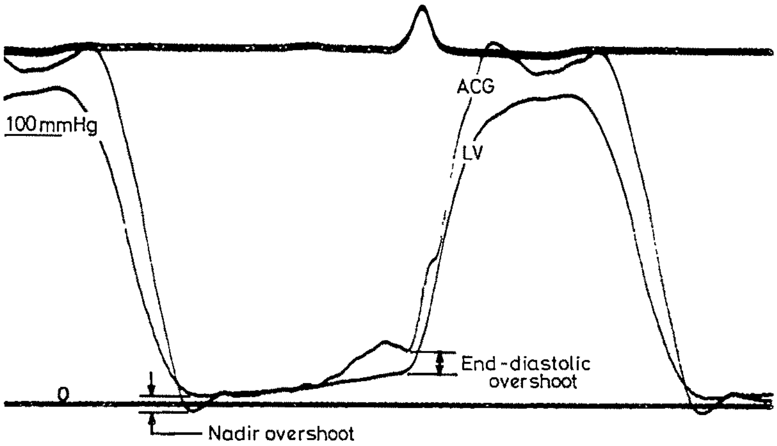

Fig. 7 Simultaneous tracings of apexcardiogram and left ventricular pressures with superimposition of pressures during slow rates of pressure change in mid-diastole. The tracing at the top is the electrocardiogram. The apexcardiogram demonstrates a negative "overshoot" in early diastole and a positive "overshoot" at end-diastole.

11 ±5 mmHg). In five and four of the 16, this overestimation by the apexcardiogram was totally accounted for by early and late diastolic "overshoots", respectively. In the remaining seven patients, overshoots occurred at both points.

SYSTOLIC PRESSURE (Fig. 8)

Left ventricular systolic pressure in 25 patients ranged from 87 to 280 mmHg (mean ±SD = 160±50 mmHg) and apexcardiographic systolic pressure varied from 60 to 684 mmHg (mean ±SD =154±129 mmHg) (r=0·69). Compared with left ventricular systolic pressure, the apexcardiograph systolic pressure was lower by 10 to 85 mmHg in 17 patients, higher by 3 to 404 mmHg in five patients, and equal in three patients. The patient with the highest left ventricular systolic pressure had an apexcardiograph systolic pressure 684 mmHg; with this patient excluded from the statistical analysis, apexcardiograph systolic pressure was significantly lower ($p < 0·025$) than intraventricular systolic pressure.

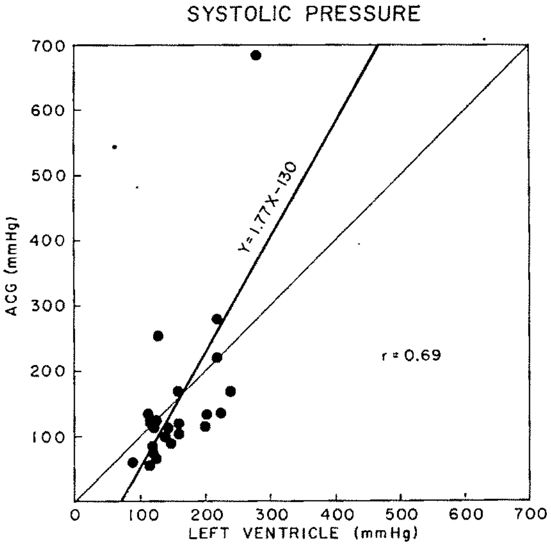

Fig. 8 Left ventricular systolic pressure versus apexcardiographic systolic pressure. The heavy solid line is the regression line and the light solid line the line of identity.

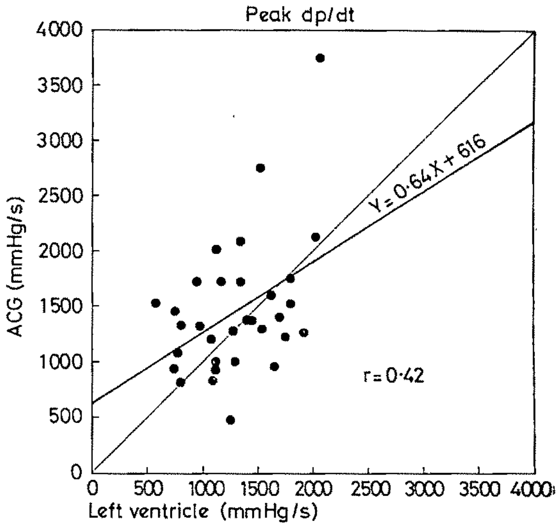

Fig. 9 Left ventricular peak dP/dt versus apexcardiographic peak dP/dt. The heavy solid line is the regression line and the light solid line the line of identity.

DP/DT (Fig. 9)

Left ventricular peak dP/dt ranged from 576 to

2062 mmHg/s (mean ±SD = 1309±408 mmHg/s) and apexcardiographic peak dP/dt ranged from 477 to 3757 mmHg/s (mean ±SD = 1456±620 mmHg/s). Correlation between the two was poor (r=0·42).

Discussion

Calibrated pressure apexcardiography employing piezo-resistive transducers has several distinct advantages: (1) it permits quantification of the apical impulse in mmHg and is essentially independent of chest wall displacement. The latter depends on chest wall compliance, which may vary from patient to patient. It should be noted, however, that the pressure perceived by the external transducer at the apex is caused by both active dynamic forces originating from cardiac motion, as well as passive transmission of ventricular pressure; (2) it permits quantification of the application or loading pressure. The pressure apexcardiographic transducer head must be applied to the chest wall with sufficient pressure so that proper coupling is obtained between it and the underlying ventricle. Since both displacement[3] and pressure[5] measured by apexcardiography have been shown to be dependent upon loading pressure, measurement of the latter is crucial for the quantification of any apexcardiographic signal; (3) the system has an infinitely long time constant (zero to 20 kHz band width), which circumvents the disadvantages of poor time-constant apexcardiographic recordings.

The method, however, has disadvantages and limitations: (a) it is not possible to record the apexcardiogram in all patients, though our experience has been that such failure occurs in patients whose apexcardiogram has not been obtainable by other techniques. (b) As with any apexcardiographic system, the position of the patient and placement of the transducer has a significant effect on the height of the signal, and both must be optimal to obtain the maximal impulse. (c) With this, our first model, we could quantify the loading pressure only in steps of 40, 80, 200, 400, and 800 mmHg. This did not allow the precise quantification which may be essential for acceptably reproducible measurements of loading pressure. (d) The transducers require careful handling since any irreversible deformation of the stainless steel diaphragm would modify the pressure calibration and any violent force applied to it (such as striking it on a hard surface) would destroy the transducer. (e) The system is relatively expensive.

When the pressure apexcardiogram was used to identify the onset of the left ventricular systolic upstroke, no significant differences in timing were found between this and internal left ventricular micromanometer pressure tracings. Previously, using fluid-filled catheter systems for recording left ventricular pressure, Inoue *et al.*[8] found that the apexcardiograph upstroke preceded the onset of left ventricular pressure rise by an average interval of 17 ms though Tavel *et al.*[9] reported no significant differences in timing. Using micromanometer catheters, Fabian *et al.*[10] also found that the left ventricular pressure upstroke followed that of the apexcardiogram by 20 ms but our data are in agreement with the findings of Manolas *et al.*[11] in humans and Willems *et al.*[12] in dogs who reported no systematic differences in timing of these two events. While there may be no significant discrepancy between groups of patients, individual variations may be based upon more than methodological error. As suggested by Tafur *et al.*[13] and Tavel *et al.*[9] the initial portion of ventricular mechanical systole may be associated with a change in ventricular configuration unaccompanied by a rise in pressure. If this change in configuration results in an outward thrust, the upstroke of the apexcardiogram may precede the left ventricular pressure rise, but if it results in retraction, then the initial rise in pressure may not be perceived by the external transducer and the upstroke of the apexcardiogram may follow that of the left ventricular pressure.

The early diastolic nadir of the left ventricular pressure trace represents an equilibration point where the pressure rise in the left ventricle resulting from filling cannot be compensated by the pressure fall caused by active relaxation. The point is not very sharp in the pressure traces of most patients, particularly when recordings are made at a high paper speed of 100 to 200 mm/s. Since the equilibration point should be equal to zero dP/dt in early diastole, measurements of the left ventricular pressure and the apexcardiogram were related to this reference point. They were identical or the apexcardiogram was earlier than the left ventricle except in a few cases. The earlier occurrence of the "0" point in the apexcardiogram may be a result of the relaxing but expanding heart causing a positive thrust on the chest wall while left ventricular pressure continues to fall.

Since there is no zero reference level, the pressure apexcardiogram is capable only of measuring *changes* in left ventricular diastolic pressure. If the externally recorded diastolic pressure changes were solely caused by passive transmission of left ventricular diastolic pressure, then both developed diastolic pressures should have been essentially equal. Though a correlation was found between apexcardiographic and left ventricular developed diastolic pressure, the former was systematically higher than the latter. Since apexcardiographic and left ventricular pressure contours appeared to be superimposable in most patients during mid-diastolic slow rates of pressure change, we attempted to determine the relative contributions of early and late diastolic overshoots to this overestimation. Examination of data in this group of patients showed that both negative early and positive late diastolic overshoots contributed to the higher developed diastolic pressure recorded in the apexcardiogram. The relative contribution of each phase varied, however, from patient to patient. In the present study, we did not attempt to determine which factors (ventricular volume, wall thickness, tension) were important in determining the magnitude and phase of these overshoots. This investigation is now possible since the loading pressure and pressure changes sensed by the apexcardiogram can be quantified.

Although a correlation was found between left ventricular and apexcardiographic systolic pressures, the latter tended to underestimate systolic pressure in the majority of patients. This probably results from loss of proper contact with the underlying ventricle as the chamber progressively decreases in size during systole. However, the apexcardiogram was higher than the left ventricular systolic pressure in five patients and this may be because of the ballistic force exerted by the heart against the chest wall during forward ejection of the stroke volume. In a few patients, these positive and negative forces may cancel each other completely so that equal systolic pressures are recorded in the apexcardiogram and left ventricle. It is possible that there would be a better correlation between internal and external pressure if they were measured at the time of aortic valve opening as suggested by Kesteloot *et al.*[14] If this were the case, there should be a good correlation between external and internal peak dP/dt. We did not find such a correlation, casting doubt on this premise.

It is clear that differences exist between left ventricular pressure and pressure measured at the apex, suggesting that the apical impulse is not simply caused by passive transmission of internal pressures. The convenient, direct method of measuring application and developed pressures at the apex described in this report permits the scientific investigation of forces responsible for the genesis of this impulse and its alteration in pathological states.

References

1 Benchimol A, Dimond EG, Carson JC. The value of the apexcardiogram as a reference tracing in phonocardiography. *Am Heart J* 1961; **61:** 485–93.

2 Benchimol A, Dimond EG. The normal and abnormal apexcardiogram. Its physiologic variation and its relation to intracardiac events. *Am J Cardiol* 1963; **12:** 368–82.

3 Mounsey JPD. Inspection and palpation of the cardiac impulse. *Prog Cardiovasc Dis* 1967; **10:** 187–206.

4 Eddleman EE, Willis K, Reeves TJ, Harrison TR. The kinetocardiogram. I. Method of recording precordial movements. *Circulation* 1953; **8:** 269–75.

5 Willems JL, DeGeest H, Kesteloot H. A new approach to the recording of low frequency precordial vibrations. *Acta Cardiol (Brux)* 1971; **26:** 263–76.

6 Gleichmann U, Kreuzer H, Loogen F, Wilke KH. Quantitative Messung von Kraft und Geschwindigkeit der Kraftenwicklung im apexkardiogramm. *Z Gesamte Exp Med* 1968; **145:** 278–88.

7 Witte J, Heublein B. The value of quantitative apexcardiography as compared to intracardiac functional diagnostics of the left ventricle. *Bibl Cardiol* 1975; **33:** 133–7.

8 Inoue K, Young GM, Grierson AL, Smulyan IT, Eich RH. Isometric contraction period of the left ventricle in acute myocardial infarction. *Circulation* 1970; **42:** 79–90.

9 Tavel ME, Campbell RW, Feigenbaum H, Steinmetz EF. The apex cardiogram and its relationship to haemodynamic events within the left heart. *Br Heart J* 1965; **27:** 829–39.

10 Fabian J, Epstein EJ, Coulshed N. Duration of phases of left ventricular systole using indirect methods. *Br Heart J* 1972; **34:** 874–81.

11 Manolas J, Rutishauser W, Wirz P, Arbenz U. Time relation between apex cardiogram and left ventricular events using simultaneous high-fidelity tracings in man. *Br Heart J* 1975; **37:** 1263–7.

12 Willems JL, DeGeest H, Kesteloot H. On the value of apex cardiography for timing intracardiac events. *Am J Cardiol* 1971; **28:** 59–66.

13 Tafur E, Cohen LS, Levine HD. The normal apex cardiogram. Its temporal relationship to electrical, acoustic, and mechanical cardiac events. *Circulation* 1964; **30:** 381–90.

14 Kesteloot H, Denef B, Willems J, DeGeest H. Relationship between the apexcardiogram and ventricular hemodynamics. In: Besse P, Bricaud H, eds. *Performance ventriculaire gauche chez l'homme: symposium de la société internationale de cardiologie, 9–10 September 1973, Bordeaux.* Paris: Expansion Scientifique, 1975: 173–83.

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Heart murmurs audible across the room in children with mitral valve prolapse

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SUMMARY Three children are described in whom an unusual heart murmur was intermittently audible in the same room without a stethoscope. Subsequent investigations disclosed mitral valve prolapse in all three patients.

A century ago, Osler[1] drew attention to heart murmurs audible at some distance from the chest wall. He described in detail an otherwise healthy 12-year-old girl with an intermittent high pitched systolic murmur, which when present was audible across the room and altered in intensity with postural changes. He was impressed by "the absence of signs of grave heart disease". An earlier description of similar unusual murmurs appeared in Germany in 1878.[2]

The aetiology of these murmurs, whether audible with or without a stethoscope, remained controversial and they were described as "whoops"[3] and later as "praecordial honks".[4] Rackley *et al.*[4] were the first to suggest that the murmurs arose from the mitral valve. Leon *et al.*[5] using intracardiac phonocardiography concluded from a study of nine patients that "these sounds were part of a spectrum of acoustical events associated with mitral incompetence".

We have recently encountered three children with similar findings to Osler's original case in whom subsequent investigations showed mitral valve prolapse.

Material and methods

M-mode echocardiography using standard techniques was performed using an Organon Teknika Ultrasonoscope interfaced with a strip chart recorder. In all the patients a 5 MHz unfocused transducer was used. Phonocardiograms were recorded on a Cambridge recorder with a 100 to 600 Hz frequency range. Ambulatory electrocardiogram monitoring was performed using an Oxford Instruments analogue recorder.

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Case reports

CASE 1

A previously healthy girl was first seen at 10 years of age with a one-year history of an intermittent sound emanating from her chest in time with the heart beat. The sound was never present when she visited her family doctor, but was loud enough to be tape recorded at home by her parents and occurred in episodes lasting from two to 20 minutes. The recording revealed a high pitched "whooping sound". Physical examination was normal apart from a short grade 2/6 systolic murmur in the mitral area. The chest *x*-ray was normal, as was the electrocardiogram apart from some minimal T wave flattening in the inferior leads. She was not considered to have significant heart disease. When she was seen again six years later, she was still well and had experienced no further episodes of the chest sound for three years. She did, however, admit to being occasionally aware of her heart beating rapidly. The physical findings were unchanged, except that a mid-systolic click was now audible. The chest *x*-ray and electrocardiogram were unchanged. Echocardiography showed late systolic prolapse of both mitral leaflets with normal dimensions of the left atrium and left ventricle. Phonocardiography confirmed the presence of a short late systolic murmur, but no click was identified. Ambulatory electrocardiogram monitoring over a 48-hour period showed sinus rhythm with occasional runs of frequent multifocal ventricular ectopic beats and short periods of coupling.

CASE 2

A healthy girl was first seen at the age of 12 years. Her general practitioner had recently detected a murmur during an examination at the time of a respiratory infection. The patient, herself, had noticed an intermittent noise from her chest during the previous three months and on several occasions it had been heard by her parents in the same room. It had been first noted after she had stretched her arms above her head and it seemed to be related to exercise. Examination was within normal limits except for a short grade 2/6 blowing mid-systolic murmur in the mitral area. The chest *x*-ray was normal as was the electrocardiogram apart from some flattened T waves in the inferior leads. When seen again 18 months later she was well but was still aware of the noise, which tended to be audible when her arms were above her head. There were no symptoms referrable to the cardiovascular system. Physical findings were unchanged except for the presence of a mid-systolic click. The chest *x*-ray and electrocardiogram were unchanged. Echocardiography demonstrated late systolic prolapse of both mitral leaflets with normal chamber dimensions, while phonocardiography identified only a mid-systolic click (Fig.). Ambulatory electrocardiogram monitoring over a 48-hour period showed sinus rhythm with very occasional unifocal ventricular ectopic beats.

CASE 3

A boy was first seen at the age of 10 years. Two years previously he had been admitted to his local hospital with a diagnosis of pericarditis. For four days before admission he had severe vomiting with diarrhoea and on the day before admission, while straining to vomit, he suddenly became aware of a squeaking noise coming from his chest. The noise was also heard by his parents on entering his bedroom and caused them great concern. While in hospital the noise occurred intermittently and seemed related to posture, and because of these features it was thought to be a friction rub. After eight weeks' bed rest he was discharged and during outpatient follow-up he remained well, but he continued to notice the noise intermittently, especially after climbing stairs or with an involuntary Valsalva manoeuvre. Examination at our clinic was within normal limits except for a grade 2/6 late systolic murmur in the mitral area. The chest *x*-ray was normal and the electrocardiogram showed T wave flattening in the inferior leads. Echocardiography showed late systolic prolapse of both mitral leaflets and increased amplitude of excursion of the anterior leaflet. The left atrial and left ventricular dimensions were normal. Phonocardiography demonstrated a quiet late systolic murmur and ambulatory electrocardiogram monitoring over a 48-hour period disclosed normal sinus rhythm.

Discussion

Mitral valve prolapse is now thought to be the most common cardiac valve disorder in adults. It has also been reported in children from the age of 2 years onwards.[6] The clinical, electrocardiographic, radiological, and echocardiographic features have been well described since its recognition as a distinct clinical entity by Barlow in 1963.[6–9] Several reviews have mentioned patients being aware of their own murmurs,[8 9] but to our present knowledge, only seven patients, including Osler's case, with murmurs loud enough to be heard across

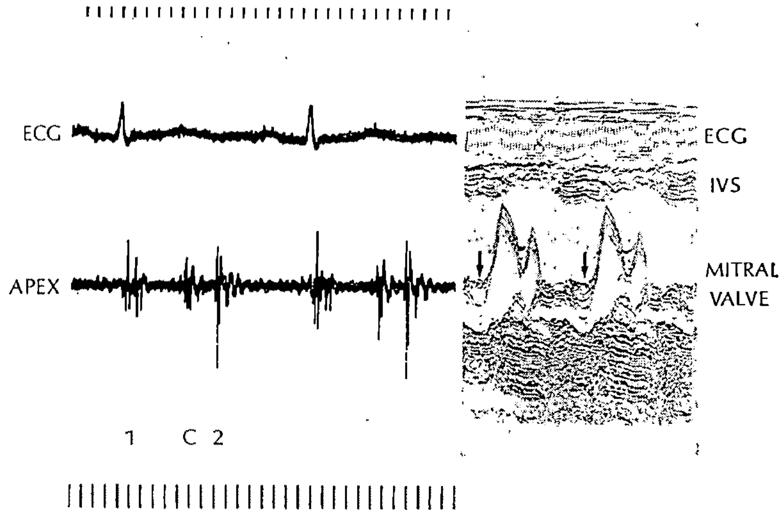

Fig. *Phonocardiogram and echocardiogram from case 2. Phonocardiogram recorded at apex demonstrates late systolic click (c). Echocardiogram demonstrates late systolic prolapse of the mitral valve—arrows. ECG, electrocardiogram; IVS, interventricular septum.*

the room, have been described in detail.[1 10–14] Six were girls ranging in age from 3 to 12 years and one was a boy aged 12 years. This female preponderance, a well-recognised feature of mitral valve prolapse, was also seen in our patients. The intermittent nature of the murmurs and their appearance on exercise or excitement are features of the mitral valve prolapse syndrome and were present in our patients. Changes in left ventricular and diastolic dimension alter the timing of the mitral valve prolapse, and volume changes alter the intensity of the murmur.

Arrhythmias, both supraventricular and ventricular, especially after exercise, are common in patients with mitral valve prolapse.[8 9] In the majority of patients, these arrhythmias are benign and not associated with symptoms, but in a few symptoms may be severe and even life threatening.[15] One of our patients (case 1) had mild symptoms associated with an arrhythmia and runs of ventricular extrasystoles were detected on ambulatory monitoring.

The original diagnosis of pericarditis in case 3 is of interest as this diagnostic error has recently been reported.[6]

It thus appears that in many patients with murmurs audible across the room there is mitral valve prolapse. Echocardiography with or without provocative manoeuvres to produce the murmur is useful in detecting such patients. Despite the many different pathological processes incriminated in the aetiology of mitral valve prolapse, the outlook in the vast majority of patients is good.[6] The risk of developing symptomatic arrhythmias or bacterial endocarditis is always present, however, and these patients require careful follow-up with antibiotic prophylaxis.

We wish to thank Drs Pugh, Morgan, and Cookson for referring the patients.

References

1 Osler W. On a remarkable heart-murmur, heard at a distance from chest-wall. *Med Times Gaz* 1880; **2:** 432–3.

2 Ebstein W. Ueber die auf grössere Entfernung vom Kranken hörbaren löne und Geräusche des Herzens und der Brustaorta. *Dtsch Arch Klin Med* 1878; **22:** 113–47.

3 McKusick VA. *Cardiovascular sound in health and disease.* Baltimore: Williams & Wilkins, 1958: 202.

4 Rackley CE, Whalen RE, Floyd WL, Orgain ES, McIntosh HD. The praecordial honk. *Am J Cardiol* 1966; **17:** 509–15.

5 Leon DF, Leonard JJ, Kroetz FW, Page WL, Shaver JA, Lancaster JF. Late systolic murmurs, clicks, and whoops arising from the mitral valve. *Am Heart J* 1966; **72:** 325–36.

6 Jeresaty RM. *Mitral valve prolapse.* New York: Raven Press, 1979.

7 Barlow JB, Pocock WA, Marchand P, Denny M. The significance of late systolic murmurs. *Am Heart J* 1963; **66:** 443–52.

8 Barlow JB, Pocock WA. The problem of non-ejection systolic clicks and associated mitral systolic murmurs: emphasis on the billowing mitral leaflet syndrome. *Am Heart J* 1975; **90:** 636–55.

9 Criley JM, Kissel GL. Prolapse of the mitral valve—the click and late systolic murmur syndrome. *Prog Cardiol* 1975; **4:** 23–36.

10 Pickering D. Clicks, whoops and honks. *Arch Dis Child* 1972; **47:** 731–4.

11 Segall HN. Autoauscultation in a patient with floppy mitral valve syndrome (letter). *Am Heart J* 1976; **91:** 269–72.

12 Lababidi Z. Floppy mitral whistle heard across the room (letter). *Am Heart J* 1976; **91:** 825.

13 Young D. Noisy floppy mitral valve (letter). *Am Heart J* 1977; **93:** 130.

14 Felner JM, Harwood S, Mond H, Plauth W, Brinsfield D, Schlant RC. Systolic honks in young children. *Am J Cardiol* 1977; **40:** 206–11.

15 Campbell RWF, Godman MG, Fiddler GI, Marquis RM, Julian DG. Ventricular arrhythmias in syndrome of balloon deformity of mitral valve. *Br Heart J* 1976; **38:** 1053–7.

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Isovolumic contraction time of right ventricle in d-transposition of great arteries*

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SUMMARY The pre-ejection period of the right ventricle in d-transposition of the great arteries is known to be prolonged, compared with the same interval of the left ventricle of normal subjects. In the present study, the echocardiographic measurement of the components of the pre-ejection period of the right ventricle of 14 patients with d-transposition of the great arteries shows that the isometric contraction time of the right ventricle in d-transposition of the great arteries is similar to the same interval calculated on the left ventricle of 76 normal children of comparable age. On the other hand, the electromechanical delay was significantly greater for the right ventricle of d-transposition of the great arteries than for the left ventricle of the normal subjects. It is concluded that the prolonged pre-ejection period of the right ventricle in d-transposition of the great arteries is not the result of right ventricular dysfunction but solely of a longer electromechanical delay.

In d-transposition of the great arteries (d-TGA), the right ventricle must maintain a normal output against the high resistance of the systemic circulation. Its ability to sustain this load throughout life has been seriously questioned since angiographic studies have shown that right ventricular end-diastolic volume is abnormally increased and the ejection fraction decreased, both before and after intra-atrial repair by the Mustard procedure.[1 2]

A recent publication on the assessment of myocardial function after Mustard's operation showed that the ratio of systolic time intervals for the right and left ventricles was appropriate for normal systemic and pulmonary ventricles, respectively.[3] On the other hand most studies on myocardial function using systolic time intervals seem to be in agreement with volume measurements and have shown a prolonged right ventricular pre-ejection period and a shortened right ventricular ejection time in d-TGA suggesting that right ventricular function was depressed.[4 5] However, these reports did not specify which part of the pre-ejection period, that is the electromechanical delay or the isovolumic contraction time, was responsible for prolonging the right ventricular pre-ejection period. Clarification of this point is essential before any conclusion can be drawn about the performance of the right ventricle. Indeed, isovolumic contraction time is the component of the pre-ejection period widely recognised as a reliable index of myocardial contractility.[6 7]

The frequent clinical observation that postoperative patients with d-TGA achieve normal physical performance without any sign of cardiac failure, and the fact that a prolonged right ventricular pre-ejection period has been found right after birth in this disease,[8] prompted us to investigate the possibility that in d-TGA, the right ventricular pre-ejection period was prolonged because of the lengthening of the right ventricular electromechanical delay.

Subjects and methods

Fourteen patients with d-TGA, surgically repaired by Mustard procedure, were included in this study. In all but two an atrial septostomy had been done previously. Their ages varied from 3½ to 16 years, with a mean of 7 years. Duration of follow-up after corrective surgery averaged three years and eight months (range: one to six years). They were all clinically asymptomatic. Associated lesions included mild pulmonary stenosis in two and a small ventricular septal defect in one. In all patients, the

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standard electrocardiogram showed right ventricular hypertrophy, without evidence of abnormal intraventricular conduction delay. Another group of 76 healthy children, aged 2½ to 16 years, with a mean of 8 years, was chosen for comparison.

In all cases echocardiograms were taken with an Echoline 20 A ultrasonoscope, coupled with a Cambridge fibreoptic recorder. An electrocardiographic lead with a well-identified Q wave was simultaneously recorded. Systolic time intervals were measured according to techniques already described.[5 9] The pre-ejection period of the systemic ventricle was calculated from the beginning of the Q wave on the electrocardiogram to the opening point of the aortic valve leaflets and identified as right ventricular pre-ejection period (RPEP) for the d-TGA group and left ventricular pre-ejection period (LPEP) for the normals. The corresponding isovolumic contraction time is, for the d-TGA, the difference between Q to aortic valve opening and Q to tricuspid valve closure (RICT) (Fig), and for the normals, the difference between Q to aortic valve opening and Q to mitral valve closure (LICT). The electromechanical delay was calculated as RPEP less RICT (REMD), and LPEP less LICT (LEMD). In the group of normal subjects, the pre-ejection period of the right ventricle was measured from the beginning of the Q wave to the opening point of the pulmonary valves; isovolumic contraction time was calculated as the difference of Q to pulmonary valve opening less Q to tricuspid valve closure, and electromechanical delay was the difference of the pre-ejection period less isovolumic contraction time. The paper speed was set as 100 mm/s, allowing measurement to the nearest 5 ms.[10] The average of at least five cardiac cycles was used in the calculations. Measurements were made at similar RR intervals.

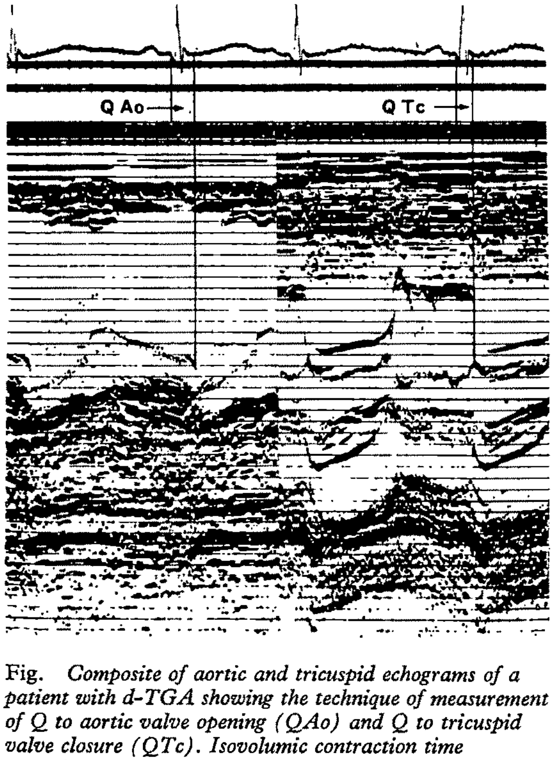

Fig. *Composite of aortic and tricuspid echograms of a patient with d-TGA showing the technique of measurement of Q to aortic valve opening (QAo) and Q to tricuspid valve closure (QTc). Isovolumic contraction time = QAo − QTc.*

In order to select the proper parametric tests for the statistical analysis of our materials, normality of the data was assessed by Lilliefors's test,[11] and equality of variances by Bartlett's test.[12] The Student's t test was then used to evaluate the difference between right ventricular pre-ejection period of the d-TGA group and left ventricular pre-ejection period of the normal subjects. A one-way analysis of variance with fixed effects was applied to compare the right ventricular isovolumic contraction time and electromechanical delay of patients with d-TGA, to the same intervals calculated on the left and right ventricular echocardiograms of the group of normal children. A contrast analysis using Scheffe's technique[13] was applied to determine the means that were significantly different.

In the group of normal subjects, the regression equations of isovolumic contraction time and electromechanical delay versus heart rate yielded weak correlation coefficients ($r = 0 \cdot 44$ and $0 \cdot 22$, respectively). This is in accordance with previous publications on the subject.[9 14] For this reason, comparisons were made between values uncorrected for heart rate.

Results

Values found for the components of the pre-ejection period of the systemic right ventricle of the 14 children with d-TGA are given in the Table, as well as the mean values for the left and right ventricles of 76 normal subjects. The mean pre-ejection period of the right ventricle of patients with d-TGA was significantly greater (98 ms, SD = 13) than the same interval for the left ventricle of normal children (79 ms, SD = 10) ($p < 0 \cdot 001$). The right ventricular isovolumic contraction time of the d-TGA was not prolonged (26 ms, SD = 5) when compared with values obtained in normal left ventricles (33 ms, SD = 8). On the other hand, the electromechanical delay of the right ventricle in d-TGA averaged 72 ms (SD = 11), while the same interval measured on the left ventricle of normal children was 46 ms (SD = 8). The difference between these two values is highly significant ($p < 0{\cdot}001$).

The average value of 72 ms found for the electromechanical delay of the right ventricle of patients with d-TGA was higher ($p < 0{\cdot}01$) than that observed in the right ventricle of our group of normals (60 ms, SD = 9). The same observation can be made for the right ventricular isovolumic contraction time in d-TGA (26 ms, SD = 5) and in normal subjects (13 ms, SD = 8) ($p < 0{\cdot}01$).

Table 1 *Pre-ejection period and its components in systemic ventricle of patients with d-TGA and in left and right ventricles of 76 normal children*

Case no.	*Age (y)*	*PEP (ms)*	*ICT (ms)*	*EMD (ms)*
Patients with d–TGA				
1	3½	100	25	75
2	4¼	80	27	53
3	5	100	20	80
4	5	92	20	72
5	5	105	25	80
6	5	80	22	58
7	5	78	28	50
8	5	103	25	78
9	7	105	30	75
10	8	85	25	60
11	9	118	38	80
12	9	110	28	82
13	10	105	25	80
14	16	110	30	80
Mean	7 Range: 3½ to 16	98 (SD 13)	26 (SD 5)	72 (SD 11)
Normal children:				
Mean LV	8 Range: 2½ to 16	79 (SD 10)	33 (SD 8)	46 (SD 8)
Mean RV	—	73 (SD 9)	13 (SD 8)	60 (SD 9)

Abbreviations: PEP, pre-ejection period; ICT, isovolumic contraction time; EMD, electromechanical delay; SD, standard deviation; LV, left ventricle; RV, right ventricle.

Comments

The ability of the right ventricle to perform adequately as a systemic pump is crucial for the long-term prognosis of patients with d-TGA having undergone intra-atrial rerouting of the venous return. Previous angiographic studies have compared volumetric parameters of the right ventricle of patients with d-TGA with those of the right ventricle of normal individuals. Abnormal values were always found.[1 2 16] In fact, the question is how the right ventricle in d-TGA compares with the left ventricle of normal individuals. Such an approach has been applied in echocardiographic studies, where right ventricular systolic time intervals of d-TGA were compared with left ventricular intervals of normal subjects. In most of these studies, the conclusion that the right ventricular function was depressed in d-TGA, was based on finding a prolonged right ventricular pre-ejection period.[4 5] The present study demonstrates that this conclusion is unwarranted. Indeed, the part of the pre-ejection period which closely correlates with measures of contractility, that is the isovolumic contraction time, is, in our group of d-TGA, similar to the same interval measured on the left ventricle of normal subjects. This finding is in full agreement with the normal pressure-velocity indices (dP/dt and derived velocity variables) previously reported for the right ventricle of d-TGA.[16 17] The apparent contradiction between our results and the data presented in the angiographic reports may be explained by the work of Peterson and co-workers,[18] who showed that changes in ejection fraction volumes and modification of the contractile state could occur independently of each other.

According to the present study, it is the prolongation of the right ventricular electromechanical delay which is responsible for the longer right ventricular pre-ejection period described in d-TGA when compared with the normal left ventricle. A previous report on time relation of dynamic events in the cardiac chambers, has documented a longer electromechanical delay for the right ventricle than for the left ventricle in normal hearts.[19] Moreover, in our study, the right ventricular electromechanical delay in d-TGA has been found to be longer than that of normal right ventricles. This could be because of the greater myocardial mass of the hypertrophied right ventricle in d-TGA, resulting in a longer ventricular activation time.[20]

We believe that serial evaluation by systolic time intervals of right ventricular function in d-TGA should be based on the measurement of the isovolumic contraction time in preference to that of the complete pre-ejection period.

References

1 Graham TP, Atwood GF, Boucek RJ, Boerth RC, Nelson JH. Right heart volume characteristics in transposition of the great arteries. *Circulation* 1975; **51:** 881–9.
2 Graham TP, Atwood GF, Boucek RJ, Boerth RC, Bender HW. Abnormalities of right ventricular function following Mustard's operation for transposition of the great arteries. *Circulation* 1975; **52:** 678–84.
3 Silverman NH, Payot M, Stanger P, Rudolph AM. The echocardiographic profile of patients after Mustard's operation. *Circulation* 1978; **58:** 1083–93.
4 Korfhagen J, Meyer R, Kaplan S. Non-invasive assessment of right ventricular performance in transposition of the great arteries (abstract). *Am J Cardiol* 1977; **39:** 310.
5 Hirschfeld S, Meyer R, Schwartz DC, Korfhagen J, Kaplan S. Measurement of right and left ventricular

systolic time intervals by echocardiography. *Circulation* 1975; **51**: 304–9.

6 Ahmed SS, Levinson GE, Schwartz CJ, Ettinger PO. Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man. *Circulation* 1972; **46**: 559–71.

7 Mason DT. Usefulness and limitations of the rate of rise of intraventricular pressure (dP/dt) in the evaluation of myocardial contractility in man. *Am J Cardiol* 1969; **23**: 516–27.

8 Fouron JC, Lombaert M, Payot M, Davignon A. Systolic time intervals during the first hours of life in D-transposition of the great arteries (abstract). Can Cardiovasc Soc, 30th Annual Meeting, Toronto.

9 Hirschfeld S, Meyer R, Korfhagen J, Kaplan S, Liebman J. The isovolumic contraction time of the left ventricle. An echographic study. *Circulation* 1976; **54**: 751–6.

10 Spodick DH, Ball HG, Pigott VM. Effects of recording speed on precision of time-based polycardiographic measurements. Optimal paper speeds for measuring points and intervals. *Br Heart J* 1978; **40**: 1344–8.

11 Lilliefors HW. On the Kolmogorov-Smirnov test for normality with mean and variance unknown. *J Am Stat Assoc* 1967; **62**: 399–402.

12 Winer BJ. *Statistical principles in experimental design.* 2nd ed. New York: McGraw-Hill, 1971: 207.

13 Scheffe H. *The analysis of variance.* New York: John Wiley, 1959: 68.

14 Spitaels S, Arbogast R, Fouron JC, Davignon A. The influence of heart rate and age on the systolic and diastolic time intervals in children. *Circulation* 1974; **49**: 1107–15.

15 Jarmakani JM, Canent RV. Preoperative and postoperative right ventricular function in children with transposition of the great vessels. *Circulation* 1974; **49** and **50**, suppl II: 39–45.

16 Godman MJ, Friedli B, Pasternac A, Kidd BSL, Trusler GA, Mustard WT. Hemodynamic studies in children four to ten years after the Mustard operation for transposition of the great arteries. *Circulation* 1976; **53**: 532–8.

17 Pasternac A, Hawker RE, Kidd L. Right and left ventricular function in complete transposition of the great arteries (abstract). *Am J Cardiol* 1973; **31**: 152.

18 Peterson KL, Skloven D, Ludbrook P, Uther JB, Ross J Jr. Comparison of isovolumic and ejection phase indices of myocardial performance in man. *Circulation* 1974; **49**: 1088–101.

19 Braunwald E, Fishman AP, Cournand A. Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. *Circ Res* 1956; **4**: 100–7.

20 Scott RC. The correlation between the electrocardiographic patterns of ventricular hypertrophy and the anatomic findings. *Circulation* 1960; **21**: 256–91.

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Exercise first-pass radionuclide ventriculography in detection of coronary artery disease

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SUMMARY Thirty-four patients with coronary artery disease were exercised on a bicycle ergometer until they developed angina. There was a highly significant fall in ejection fraction from a mean of 61·1 to 52·9 which was more pronounced in the group with three vessel coronary artery disease. A coronary index was computed which took into account the extent and distribution of coronary artery lesions. Those patients with an index $<0·3$ (that is more severe disease) had greater falls in ejection fraction than those with higher indices. All five patients in whom there was a fall in ejection fraction of 15 per cent or more had triple vessel disease. Wall motion abnormalities were assessed by a hemiaxial method. Of 34 exercise-induced zones of wall motion abnormalities, 32 were in regions supplied by significantly stenosed coronary arteries.

A test was defined as positive if there was an abnormal exercise ejection fraction ($<50\%$), an exercise-induced wall motion abnormality, or a fall in ejection fraction at angina of at least 10 per cent. Of the 19 patients with triple vessel disease, 18 (95%) had a positive result, as did 11 of 15 (73%) patients with one or two vessel disease. A group of eight patients with normal coronary arteries were also exercised and in none of these was there a positive result. Exercise first-pass radionuclide ventriculography demonstrates changes in global and regional ventricular function in patients with coronary artery disease which are not present in normal subjects. It may also help to identify patients at high risk.

Since the main symptoms of ischaemic heart disease are present only at exercise, in recent years greater emphasis has been placed on the performance of the heart during stress. In the cardiac catheterisation laboratory both atrial pacing[1 2] and hand grip exercise[3] have been used to induce ischaemia. Sharma and Taylor[4] reported a fall in ejection fraction on dynamic exercise in patients with coronary artery disease undergoing cardiac catheterisation.

Radionuclide ventriculography is a non-invasive procedure which allows exercise to be performed under more physiological conditions. Borer *et al.*,[5] using equilibrium gated blood pool scanning in a modified left anterior oblique projection, demonstrated a fall in ejection fraction in patients exercised to angina. Bodenheimer *et al.*,[6] using the first-pass technique, also reported changes in regional ejection fraction in patients with ischaemic heart disease during hand grip exercise.

First-pass radionuclide ventriculography has been validated against contrast angiograms in the detection of regional and general wall motion abnormalities at rest[7] and induced by pacing to angina.[8]

This study reports the changes in regional wall motion and ejection fraction induced by dynamic exercise to angina. It relates these changes to the extent and distribution of coronary artery lesions.

Patients and methods

Thirty-four patients were studied. There were 33 men and one woman whose ages ranged from 33 to 67 years (mean 51). All patients were being investigated for angina and underwent cardiac catheterisation. Beta-blocking drugs were stopped 48 hours before the investigation. Informed consent was obtained in every case. Eight control patients with normal coronary arteries were also investigated.

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EXERCISE STUDIES

The patients were positioned under the detector of the multicrystal gamma camera (Baird Atomic, System 77) in the 20° right anterior oblique projection and the electrocardiogram leads attached (standard lead I). An intravenous cannula was inserted into an antecubital vein, preferably in the right arm. The feet of the patient were placed on the bicycle pedals and correct positioning ascertained by injecting a 1 mCi bolus of technetium-99^m, as pertechnetate, with a saline flush. Electrocardiographic monitoring was carried out throughout the procedure.

The patients were then exercised on the bicycle ergometer in the supine position. The workload was increased by 25 watt increments every two minutes until the patient began to complain of angina. When the pain has reached moderate severity, the patient was asked to stop pedalling. A 10 mCi bolus of technetium-99^m was injected with a rapid saline flush and counting was carried out for 50 seconds at a framing rate of 20 per second. Data were collected on to disc and stored on magnetic tape, correction having been made for dead-time of the instrument and for flood field non-uniformity.

Twenty minutes later a static background frame of residual blood pool activity was counted with the patient in the same position as previously. Immediately afterwards the resting study was performed with a 15 mCi bolus. This was corrected for residual blood pool background activity as well as for dead-time and non-uniformity before storage on magnetic tape.

CORONARY ANGIOGRAPHY

Coronary angiograms were performed by either the Sones or Judkins technique and coronary lesions were assessed by an independent observer.

DATA ANALYSIS

Radionuclide angiography

After transferring the data from tape to disc, serial frames of each study were summated over 1·5 second intervals and the left ventricular phase identified. A region of interest was selected over the left ventricle with a magnetic pen and grid array representing the 294 crystals of the detector. A time activity curve was generated and a background frame was selected from the pulmonary phase. Spatial and temporal correction were then automatically made during all further data processing for the exponential decay of lung activity. The peaks and troughs of the left ventricular phase, which represent end-diastole and end-systole, respectively, of each cardiac cycle, were used to derive ejection fraction and a representative cardiac cycle as previously described.[9] End-systolic and end-diastolic images were obtained from this representative cycle and used to generate ventricular perimeters. This was achieved by an edge enhancement technique whereby the band of counts from 25 to 30 per cent of the maximum count (N max) in any one cell was isolated and normalised to the image with the lower N max. The end-diastolic perimeters were then superimposed so that regional wall motion could be assessed.

Wall motion abnormalities were quantified by a hemiaxial method as used by Stone *et al.*[8] This method was based on that described by Dwyer[10] and Leighton *et al.*[11] The long axis of the ventricle was drawn from the mid-point of the aortic valve plane to the apex. It was then trisected, and perpendiculars drawn from the points one-third and two-thirds of the distance along it to the ventricular perimeters at end-systole and end-diastole. Five hemiaxes were generated: two anterior, one apical, and two inferior, and the percentage shortening of each hemiaxis was calculated. The normal range of shortening of each hemiaxis was derived from the radionuclide ventriculograms of 22 patients without heart disease who were studied at rest (Table 1).

Hypokinesis of any hemiaxis was defined as a percentage shortening of less than two standard deviations below the mean percentage shortening of that hemiaxis in the normals. Akinesis was defined as absence of shortening of a given hemiaxis.

Table 1 *Normal ranges of shortening for hemiaxial model*

Hemiaxis	*Percentage shortening (mean ±2SD)*
1	21–85
2	51–100
3	47–100
4	45–100
5	26–89

CORONARY ANGIOGRAMS

Coronary lesions were graded visually from 0 to 4, where grade 0 = normal; grade 1 = 25 per cent stenosis; grade 2 = 50 per cent stenosis; grade 3 = 75 per cent stenosis; and grade 4 = occlusion.

The extent of coronary disease was classified by two methods:

(1) Conventional separation into single, double, or triple vessel disease, where any lesion of grade 2 or more (that is greater than 50%) was regarded as a significant stenosis.

(2) In order to make greater allowance for position and extent of lesions a coronary index was computed by the method of Balcon *et al.*[12]

For the calculation of the index, the coronary tree was divided into 13 anatomical sections (Fig. 1). Each section was weighted according to size of lesion within it by the formula:

$$\mathrm{Wi} = 1 - \frac{\mathrm{Gi}}{4}$$

Where Wi is the weighting of the lesion in the *i*th section, Gi is the grading of the lesion in the *i*th section.

Thus the weighting is zero for an occluded segment and 1 for a patent one. An index was then calculated for each coronary artery separately:

LCI (left coronary index)

$$= \frac{W_1[W_2 \times W_3(W_4+W_5)+W_6(W_7+W_8+W_9)]}{5}$$

RCI (right coronary index)

$$= \frac{W_{10}(W_{11}+W_{12}+W_{13})}{3}$$

TCI (total coronary index)

$$= \frac{5 \times \mathrm{LCI}+3 \times \mathrm{RCI}}{8}$$

Thus allowance is made for the contribution of each vessel to total myocardial supply. In addition, because of multiplication of serial lesions, proximal stenoses will have proportionately greater effect.

The divisors in the formulae for the calculation of the individual indices are the number of terminal vessels. A normal system scores 1, and the index progressively declines towards 0 as obstruction increases. If certain vessels are not present, the individual indices and final calculation are adjusted accordingly.

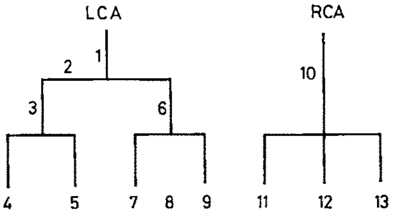

Fig. 1 *Model of coronary tree for computation of index (1, left main stem; 2, 3, 4, divisions of left anterior descending; 5, diagonal; 6, main circumflex; 7, 8, 9, lateral circumflex branches; 10, right coronary artery; 11, 12, 13, inferior left ventricular branches from right coronary artery).*

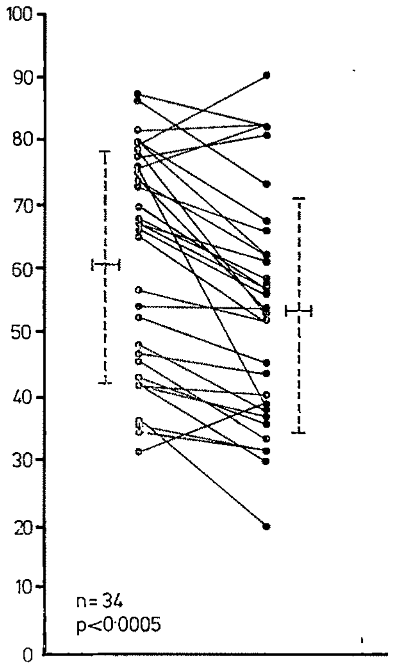

Fig. 2 *Exercise-induced change in ejection fraction.*

Results

CORONARY LESIONS

There were 19 patients with triple vessel disease, two of whom also had a significant left main stem stenosis, 10 with double vessel disease, and five with single vessel disease. Coronary index ranged from 0·075 to 0·875. Seventeen patients had an index less than 0·3, and 17 an index higher than 0·3.

GLOBAL LEFT VENTRICULAR FUNCTION

The change in ejection fraction on exercise in all 34 patients with coronary artery disease is shown in Fig. 2. Mean ejection fraction fell from 61·1 per cent at rest to 52·9 per cent on exercise. This change was highly significant ($p < 0{\cdot}0005$). In 27 patients ejection fraction fell, in four it rose, and in three it remained unchanged. In the eight normal patients who were also exercised, mean ejection fraction rose from 72·1 to 73·5 per cent. The patients with triple vessel disease had a highly significant fall in ejection fraction on exercise from a mean of 59·3 to

47·9 per cent ($p < 0·005$). Though the group with single and double vessel disease also had a significant fall in ejection fraction from a mean of 63·3 to 59·4 per cent ($p < 0·05$), this was significantly less than for the group with triple vessel disease ($p < 0·01$) (Fig. 3). In 16 of the 19 patients with triple vessel disease ejection fraction fell on exercise and in three it remained unchanged. All five patients with a fall in ejection fraction of greater than 15 per cent had triple vessel disease. This subgroup contains the two patients with a significant left main stem stenosis.

Patients with an index less than 0·3 (that is the more extensive disease) had a highly significant fall in ejection fraction from 61·7 to 49·4 per cent ($p < 0·0005$). Again, this fall was significantly greater ($p < 0·005$) than that which occurred in the group with indices of over 0·3 (Fig. 4). All 17 patients with a coronary index of less than 0·3 had a fall in ejection fraction on exercise to angina.

WALL MOTION CHANGES

Thirty-four areas of wall motion abnormality were induced by exercise. Of these, 10 were anterior, 13 apical, and 11 inferior in location. All 10 patients who developed anterior wall motion changes had significant lesions in the anterior descending coronary artery. Of the 13 patients who developed apical wall motion abnormalities, 12 had lesions in either the anterior descending or circumflex systems. Of the 11 patients who developed inferior zones of wall motion abnormalities on exercise to angina, 10 had a lesion in either the right coronary artery or the atrioventricular branch of a dominant left circumflex system. Thus, of the 34 areas of exercise-induced wall motion abnormalities, 32 were in regions supplied by significantly stenosed coronary arteries (Table 2).

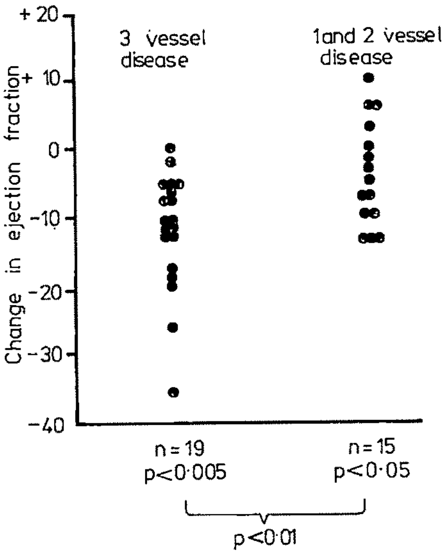

Fig. 3 *Exercise-induced change in ejection fraction for single, double, and triple vessel disease.*

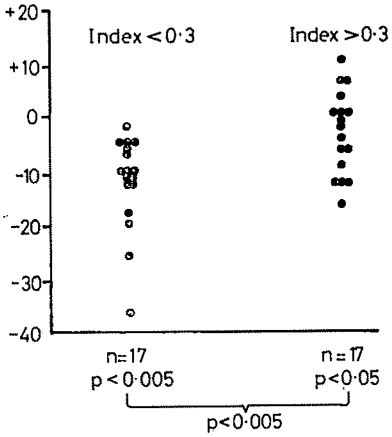

Fig. 4 *Exercise-induced change in ejection fraction: coronary index.*

Table 2 *Exercise-induced areas of wall motion abnormality*

	Number	*Subtended by coronary lesion*
Anterior	10	10
Apical	13	12
Inferior	11	10
Total	34	32

COMBINED ANALYSIS

The combination of ejection fraction and regional wall motion data allows improved identification of patients with coronary artery disease (Table 3). We have defined a positive result as an exercise-induced wall motion abnormality, an abnormal exercise left

Table 3 *Combined analysis in detection of coronary disease*

	No induced WMA, normal exercise LVEF, change in LVEF < 10 per cent fall	*Induced WMA or abnormal exercise LVEF or fall in LVEF ⩾10 per cent*
Normal (8)	8 (100%)	0 (0%)
Single and double vessel disease (15)	4 (27%)	11 (73%)
Triple vessel disease (19)	1 (5%)	18 (95%)

WMA, wall motion abnormalities; LVEF, left ventricular ejection fraction.

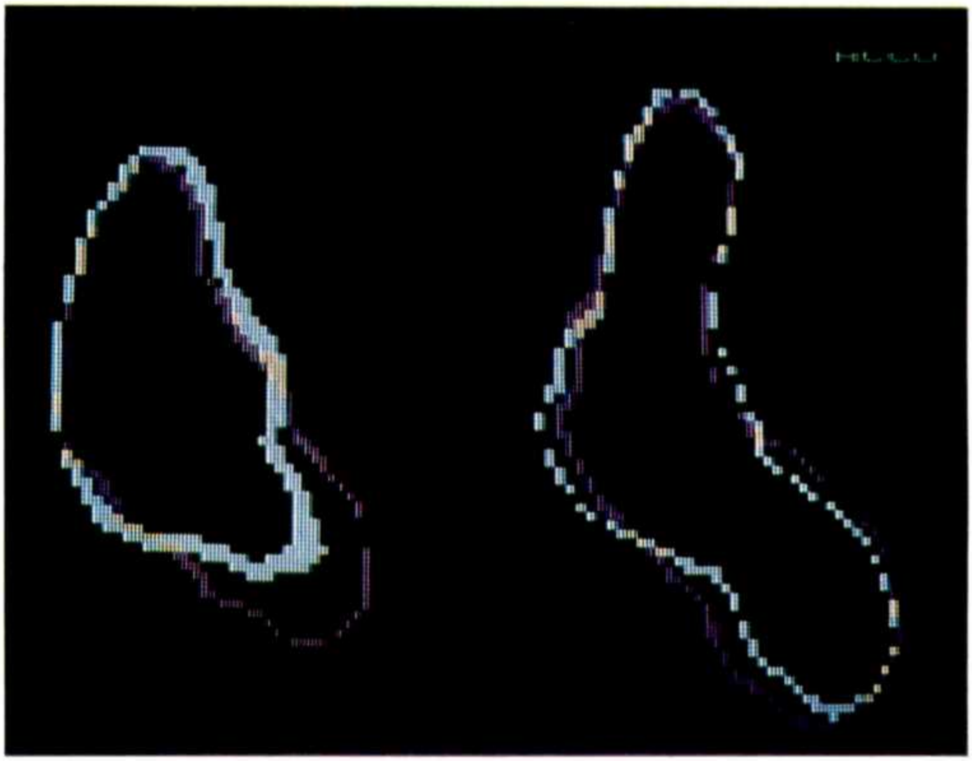

Fig. 5 *Exercise-induced change in ventricular function in a patient with triple vessel disease. End-diastolic perimeter: mauve; end-systolic perimeter: turquoise.*

ventricular ejection fraction (<50%), or a fall in ejection fraction of at least 10 per cent on exercise. No normal patient had a positive result. Of 15 patients with single and double vessel disease, 11 had a positive result (73%). Of the 19 patients with triple vessel disease, 18 (95%) had a positive result and only one a negative test. Of the 17 patients with an index of less than 0·3, 16 had a positive result as did 12 of the 17 whose index was greater than 0·3.

Fig. 5 shows the change in ventricular function induced by exercise to angina, in a patient with triple vessel disease. The end-diastolic perimeters are mauve in colour and the end-systolic perimeters turquoise. On the left is the resting study which shows symmetrical inward wall motion from the end-diastolic to the end-systolic perimeter. The study performed during exercise is shown on the right. There is extensive wall motion abnormality with apical akinesis and anterior and inferior hypokinesis. Ejection fraction fell from 75 per cent at rest to 39 per cent on exercise.

Discussion

It is accepted that impairment of left ventricular function occurs with the onset of ischaemia,[13 14] but the investigation of ventricular function in patients with coronary artery disease has been mainly directed towards catheter laboratory studies at rest.[15 16] Sharma and Taylor[4] showed a fall in ejection fraction on exercise during cardiac catheterisation, but did not investigate wall motion changes or relate their findings to extent of coronary disease.

By its very nature, exercise during cardiac catheterisation is an invasive and difficult procedure. The application of non-invasive radionuclide techniques to cardiology has allowed the assessment of cardiac function to be made during dynamic exercise tests which represent a more physiological state. Myocardial perfusion scintigraphy with thallium-201 is widely used,[17 18] but there have been recent reports of its limitations.[19–22] Though Borer *et al.*[5] report falls in ejection fraction in patients exercised to angina and investigated by equilibrium gated technique, in their study there was no quantitative assessment of wall motion abnormalities and no attempt was made to relate the changes seen to extent of coronary artery disease.

First-pass ventriculography offers certain advantages over the gated technique. Firstly, the rapid data acquisition time allows the assessment of contraction to take place over a very short period and therefore represents the function of the left ventricle at true exercise end-point. Secondly, since the right and left ventricles do not contain counts simultaneously, the right anterior oblique projection may be used. This is superior to the left anterior oblique in the assessment of regional wall motion in ischaemic heart disease.[7] [23–25] The first-pass technique has also been able to demonstrate wall motion changes at rest[7] and pacing to angina[8] which correlate with contrast angiography.

In this study we have shown that falls in ejection fraction may be shown by first-pass technique in patients with coronary artery disease. These falls were significantly greater for the group of patients with more extensive lesions. The five patients whose ejection fraction fell by more than 15 per cent all had triple vessel disease (including two with significant left main stem stenosis).

The use of coronary index to score lesions allows for the greater influence of proximal lesions on myocardial blood supply and also provides an overall assessment of the extent of coronary artery obstructions. Previous investigations have shown no relation between resting left ventricular function and a coronary score.[16] The index used in the present study was described by Balcon *et al.*[12] and has been correlated with prognosis and exercise tolerence in patients with coronary disease. In this study the degree of change of ejection fraction seen at angina was higher for those patients with a lower coronary index, indicating that stress ventriculography unmasks the effect of coronary lesions on myocardial performance.

A possible criticism of the methods is that two consecutive studies were analysed and that a consistent error might be introduced by always performing the exercise study before the resting one. However, Marshall *et al.*[25] and Bodenheimer *et al.*[7] have shown good agreement between successive first-pass investigations and that the order in which the respective obliques were used in a biplane study did not affect the results. Also the present study shows good separation between the groups of patients, all of whom were studied in the same way.

Wall motion abnormalities were analysed by a hemiaxial method based on that of Leighton *et al.*[11] Bodenheimer *et al.*[7] used a similar method for resting nuclear angiograms and found a good correlation with contrast angiography. We have also reported previously a good correlation between nuclear and contrast angiography for pacing-induced wall motion abnormalities assessed by this hemiaxial model.[8]

There was an excellent association in this study between the region of wall motion abnormality and the site of coronary artery stenosis. Of 34 abnormal segments of contraction induced by exercise, 32 were in regions supplied by significantly stenosed coronary arteries. The regional information supplied by the technique depends on the use of the multi-crystal gamma camera and should prove valuable, perhaps in combination with perfusion studies, in the assessment of the effects of interventions such as saphenous vein bypass surgery.

The combination of regional wall motion and ejection fraction data improved identification of patients with coronary disease. Eighteen of 19 patients with triple vessel disease had a positive exercise study and the overall success rate in the identification of patients with coronary artery disease was 29 of 34 (87·5%). Thus the ability of this technique to demonstrate regional wall motion changes in the right anterior oblique projection is vital if the method is used in the screening of patients with coronary disease. The results are especially important in view of recent doubts about the ability of myocardial perfusion scintigraphy with thallium-201 to identify patients with triple vessel disease.[20–22]

Exercise first-pass radionuclide ventriculography is a non-invasive technique which provides regional and global assessment of ventricular function during angina. It should prove valuable in the screening and study of patients with ischaemic heart disease and may identify patients at high risk.

References

1 O'Brien KP, Higgs LM, Glancy DL, Epstein SE. Hemodynamic accompaniments of angina. *Circulation* 1969; **39:** 735–43.

2 Rickards A, Seabra-Gomes R, Thurston P. The assessment of regional abnormalities of the left ventricle by angiography. *Eur J Cardiol* 1977; **5:** 167–82.

3 Krayenbuehl HP, Schoenbeck M, Rutishauser W, Wirz P. Abnormal segmental contraction velocity in coronary artery disease produced by isometric exercise and atrial pacing. *Am J Cardiol* 1975; **35:** 785–94.

4 Sharma B, Taylor SH. Localisation of left ventricular ischaemia in angina pectoris by cineangiography during exercise. *Br Heart J* 1975; **37:** 963–70.

5 Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS. Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary-artery disease. *N Engl J Med* 1977; **296:** 839–44.

6 Bodenheimer MM, Banka VS, Fooshee CM, Gillespie JA, Helfant RH. Detection of coronary heart disease using radionuclide determined regional ejection fraction at rest and during handgrip exercise; correlation with coronary arteriography. *Circulation* 1978; **58:** 640–8.

7 Bodenheimer MM, Banka VS, Fooshee CM, Hermann GA, Helfant RH. Quantitative radionuclide angiography in the right anterior oblique view: comparison with contrast ventriculography. *Am J Cardiol* 1978; **41:** 718–25.

8 Stone D, Dymond D, Elliott AT, Britton KE, Spurrell RAJ, Banim SO. Use of first-pass radionuclide ventriculography in assessment of wall motion abnormalities induced by incremental atrial pacing in patients with coronary artery disease. *Br Heart J* 1980; **43:** 369–75.

9 Dymond DS, Jarritt PH, Britton KE, Spurrell RAJ. Detection of post-infarction left ventricular aneurysms by first-pass radionuclide ventriculography using a multicrystal gamma camera. *Br Heart J* 1979; **41:** 68–78.

10 Dwyer EM Jr. Left ventricular pressure-volume alterations and regional disorders of contraction during myocardial ischemia induced by atrial pacing. *Circulation* 1970; **42:** 1111–22.

11 Leighton RF, Wilt SM, Lewis RP. Detection of hypokinesis by a quantitative assessment of left ventricular cineangiograms. *Circulation* 1974; **50:** 121–7.

12 Balcon R, Cattell MR, Stone DL, Fuerlicht J. A computer generated index for the assessment of coronary angiography. *Acta Med Scand* 1978; **615,** suppl: 25–30.

13 Tennant R, Wiggers CJ. Effect of coronary occlusion on myocardial contraction. *Am J Physiol* 1935; **112:** 351–61.

14 Banka VS, Helfant RH. Temporal sequence of dynamic contractile characteristics in ischemic and non-ischemic myocardium after acute coronary ligation. *Am J Cardiol* 1974; **34:** 158–63.

15 Bruschke AVG, Proudfit WL, Sones FM Jr. Progress study of 590 consecutive non-surgical cases of coronary disease followed 5–9 years. *Circulation* 1973; **47:** 1154–63.

16 Björk L, Cullhed I, Hallén A. Cineangiographic studies of the left ventricle in patients with angina pectoris. *Circulation* 1967; **36:** 868–77.

17 Hamilton GW, Trobaugh GB, Ritchie JL, Williams DL, Weaver WD, Gould KL. Myocardial imaging with intravenously injected Thallium-201 in patients with suspected coronary artery disease. *Am J Cardiol* 1977; **39:** 347–54.

18 Botvinick EH, Taradash MR, Shames DM, Parmley WW. Thallium-201 myocardial perfusion scintigraphy for the clinical clarification of normal, abnormal, and equivocal electrocardiographic stress tests. *Am J Cardiol* 1978; **41:** 43–51.

19 Mueller TM, Marcus ML, Ehrhardt JC, Chaudhuri T, Abboud FM. Limitations of Thallium-201 myocardial perfusion scintigrams. *Circulation* 1976; **54:** 640–6.

20 McKillop JH, Murray RG, Turner JG, Bessent RG, Lorimer AR, Greig WR. Can the extent of coronary artery disease be predicted from Thallium-201 myocardial images? *J Nucl Med* 1979; **20;** 715–9.

21 Pierson RN, Alam S, Kemp HG, Friedman MI. Radiocardiography in clinical cardiology. *Semin Nucl Med* 1977; **7:** 85–100.

22 Corne RA, Gotsman MS, Atlan H. Radionuclide assessment of regional myocardial perfusion with thallium-201. *Am Heart J* 1979; **97:** 112–8.

23 Jengo JA, Oren V, Conant R, *et al.* Effects of maximal exercise stress on left ventricular function in patients with coronary artery disease using first pass radionuclide angiocardiography. A rapid, non-invasive technique for determining ejection fraction and segmental wall motion. *Circulation* 1979; **59:** 60–65.

24 Cohn PF, Gorlin R, Adams DF, Chahine RA, Vokonas PS, Herman MV. Comparison of biplane and single plane left ventriculograms in patients with coronary artery disease. *Am J Cardiol* 1974; **33:** 1–6.

25 Marshall RC, Berger HJ, Costin JC, *et al.* Assessment of cardiac performance with quantitative radionuclide angiocardiography. *Circulation* 1977; **56:** 820–9.

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Br Heart J 1980; **44:** 215–20

Effect of vasodilator drugs on exercise performance in cardiac failure

Comparison of hydralazine and prazosin

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SUMMARY Although vasodilator drugs cause haemodynamic improvement at rest, their effect on the overall exercise response is uncertain. Nine patients with severe diuretic dependent cardiac failure were studied before and during upright bicycle exercise, after the double blind administration of equihypotensive doses of hydralazine (H) 75 mg, prazosin (Pr) 3 mg, and placebo (Pl). The ventilatory response and oxygen uptake were monitored continuously. Cardiac output was measured during the third minute of steady state exercise by the CO_2 rebreathing method.

At rest when the treatment groups were compared with placebo, there was a 25 per cent increase in cardiac index, placebo $1{\cdot}9 \pm 0{\cdot}1$, hydralazine $2{\cdot}3 \pm 0{\cdot}1$, prazosin $2{\cdot}4 \pm 0{\cdot}1$, and 23 per cent decrease in the arteriovenous oxygen content difference, placebo $9{\cdot}1 \pm 0{\cdot}7$, hydralazine $7{\cdot}3 \pm 0{\cdot}4$, and prazosin $6{\cdot}9 \pm 0{\cdot}7$ ml O_2/100 ml. After progressive exercise to symptom limited maximum, there was no significant difference in the exercise duration, oxygen uptake, peak heart rate, or blood pressure. Even during steady state exercise (at two-thirds maximum), heart rate, blood pressure, cardiac index, stroke volume, stroke work, and arteriovenous oxygen content did not differ in the treatment or placebo periods.

After the acute oral administration of hydralazine or prazosin in doses which produce a significant haemodynamic improvement at rest, there were no changes in the cardiorespiratory response during exercise.

Vasodilator drugs are effective in both short- and long-term treatment of patients with severe heart failure.[1–3] Though their effects on resting haemodynamics are well defined, it is not yet clear whether they improve the exercise performance of such patients. Some reports have suggested an improvement in exercise capacity and haemodynamic reserves after the acute administration of a vasodilator drug,[4 5] whereas others showed no change in maximal exercise capacity, but improved pump function at submaximal workloads.[6]

In the present study, we have compared the effects of the predominantly arteriolar vasodilator hydralazine with the arteriolar and venodilator agent prazosin on the cardiac output and ventilatory responses during maximal and steady state exercise and on the time over which such exercise can be tolerated.

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Patients and methods

Nine patients with chronic congestive heart failure and class II to III symptomatology (New York Heart Association criteria) were included in the study. Their ages ranged from 27 to 65 years (mean 47 years); seven were men and two were women. All were taking optimal doses of diuretics and digoxin which were continued in unchanged doses throughout the study. The patients' symptoms and weight were also unchanged for four weeks before the study.

Heart failure was attributed to coronary artery disease in three patients, hypertension in one, cardiomyopathy in four, and mitral valve replacement with poor left ventricular function in one. No patient had severe angina pectoris, recent myocardial infarction (less than six months), or significant mitral regurgitation.

Table 1 *Observations at rest (seated on bicycle ergometer)*

Case no.	*Oxygen uptake (ml/min)*			*Heart rate (b/min)*			*Mean arterial pressure (mmHg)*			*Cardiac index (l/min per m²)*			*Stroke volume index (ml/m²)*		
	Pl	*H*	*Pr*	*Pl*	*H*	*Pr*	*Pl*	*H*	*Pr*	*Pl*	*H*	*Pr*	*Pl*	*H*	*Pr*
1	385	404	364	84	93	96	80	73	80	2·2	2·3	2·2	26	25	23
2	249	279	299	122	117	132	86	87	80	1·3	2·9	2·7	12	25	21
3	333	284	265	114	108	93	90	80	63	1·6	2·7	1·7	15	25	18
4	387	323	356	108	112	120	97	86	86	1·8	2·5	3·1	17	22	26
5	340	274	317	114	114	114	86	80	90	2·6	2·4	2·4	23	21	21
6	233	314	313	72	84	70	83	88	82	2·3	2·1	2·3	32	25	33
7	204	211	150	75	78	85	113	117	96	1·5	1·7	2·0	20	20	24
8	282	275	248	100	110	100	80	86	86	2·3	2·2	2·3	23	20	33
9	237	371	20	72	75	75	87	90	68	1·9	1·6	2·1	26	21	28
Mean	294	303	281	96	99	98	89	87	81	1·9	2·3	2·4	22	23	25
SE	24	20	24	7	6	6	4	4	4	0·1	0·1	0·1	2	1	2
p		NS	NS		NS	NS		NS	NS		NS	$<0·05$		NS	$<0·05$

SE, Standard error of mean; NS, $p<0·05$.
Pl, placebo; H, hydralazine; Pr, prazosin.

The exercise studies were performed on three mornings within seven days. The patients attended the hospital after taking a light breakfast. Informed written consent was obtained from all patients.

DATA COLLECTION AND ANALYSIS

Heart rate and electrocardiogram were monitored continuously and blood pressure was measured at one-minute intervals by sphygmomanometer. Inspired air volumes were measured continuously with a Parkinson Cowan gas meter linked to a linear potentiometric resistor. Expired air passed through a mixing chamber from which a continuous aliquot was withdrawn for measurement of carbon dioxide content using a Beckman Medical Gas Analyzer LB2 and oxygen content using a Beckman Oxygen Analyzer OM11. The outputs from the gas meter potentiometer and the gas analysers were recorded continuously on a Sanborn 350 chart recorder. Cardiac output was measured during steady state exercise using the carbon dioxide rebreathing method. This method has been shown to compare well with dye dilution methods of determining cardiac output.[7] It provides reliable measurements of cardiac output both at rest and during exercise in patients with congestive heart failure.[8]

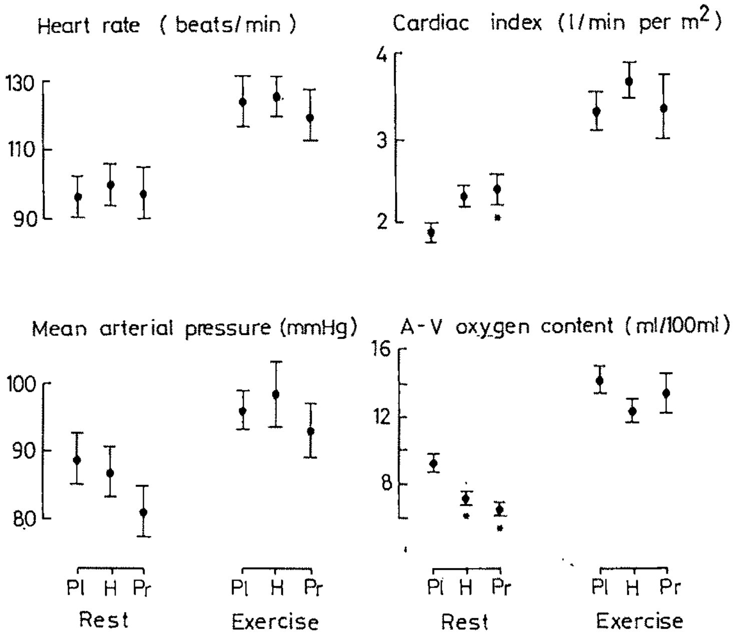

Fig. *The effects of placebo (Pl) hydralazine (H), and prazosin (Pr), on the heart rate, mean arterial pressure cardiac index, arteriovenous (A-V) oxygen content at rest and during steady state exercise.*

Systemic vascular resistance (dynes s cm^{-5})			*Arteriovenous oxygen (ml/100 ml)*		
Pl	*H*	*Pr*	*Pl*	*H*	*Pr*
1454	1242	1422	8·8	8·6	8·1
3621	1546	1600	13·1	6·2	7·5
2544	1308	1641	11·6	5·9	11·4
2236	1421	1150	10·6	6·4	5·2
1496	1561	1714	7·4	6·7	7·5
1660	2011	1640	8·8	7·9	7·8
3348	3600	2560	7·6	8·1	5·0
1488	1638	1104	6·6	6·5	4·0
2109	1714	1360	7·2	8·8	5·5
2217	1782	1461	9·1	7·1	6·9
±271	240	214	0·7	0·4	0·9
	$<0{\cdot}05$	$<0{\cdot}01$		$<0{\cdot}05$	$<0{\cdot}005$

Mean arterial pressure was calculated from the diastolic pressure plus one-third of the pulse pressure. Arteriovenous oxygen content difference was calculated from the oxygen uptake divided by the cardiac output. Systemic vascular resistance (dynes s cm^{-5}) was calculated from mean arterial pressure divided by the cardiac output multiplied by 80.

Statistical analysis between groups was performed using Student's paired t test.

METHOD OF STUDY

The patients attended the hospital at the same time on three mornings within the same week. The order of the oral treatment was selected by a random double blind design. In order to avoid first dose effects, one capsule was given on the evening before each study, which contained the same drug as administered on the morning of the study. Each capsule contained either prazosin 1 mg, hydralazine 25 mg, or placebo.

The exercise study started two hours after the administration of three capsules (that is hydralazine 75 mg or prazosin 3 mg or placebo). Exercise was performed seated on a bicycle ergometer (Elema Schonander). Starting at a workload of 200 kpm/min, work was increased by 50 kpm every one minute until terminated by fatigue or dyspnoea. One exercise study was stopped prematurely because of frequent ventricular extrasystoles; this was excluded from the analysis.

After resting for 30 minutes, the patient exercised for four minutes to a steady state of oxygen consumption at a workload of approximately 60 per cent of the highest load previously attained and the same workload was used in the subsequent two studies. Haemodynamic and ventilatory measurements were made during the final minute of exercise on each occasion.

Results

RESTING MEASUREMENTS

The effects of hydralazine and prazosin are compared with placebo for the resting patient seated on the bicycle ergometer (Table 1 and Fig.). Cardiac index increased significantly after prazosin from 1·9 ±0·1 to 2·4 ±0·1 l/min per m^2 ($p<0{\cdot}05$), but after hydralazine the increase did not achieve statistical significance. Systemic vascular resistance was reduced from 2217 ±271 to 1782 ±140 dynes s cm^{-5} after hydralazine ($p<0{\cdot}05$) and to 1461 ±214 dynes s cm^{-5} after prazosin ($p<0{\cdot}01$). The arteriovenous oxygen content difference decreased in both treatment groups (9·1 ±0·7 ml/100 ml versus hydralazine 7·1 ±0·4 ml/100 ml ($p<0{\cdot}05$) and prazosin 6·9 ±0·9 ml/100 ml ($p<0{\cdot}005$)).

PROGRESSIVE EXERCISE

The values in Table 2 represent the individual maxima attained on each treatment at the peak

Table 2 *Observations at maximal exercise*

Case no.	*Maximal oxygen uptake (ml/kg per min)*			*Peak heart rate (b/min)*			*Peak ventilation (l/min)*			*Duration of exercise (min)*		
	Pl	*H*	*Pr*	*Pl*	*H*	*Pr*	*Pl*	*H*	*Pr*	*Pl*	*H*	*Pr*
1	14·5	14·9	12·5	108	114	111	62	62	58	5·1	6·6	5·5
2	12·4	12·5	12·0	141	138	144	49	51	37	3·7	4·1	2·6
3	14·5	15·4	10·8	132	126	112	81	77	43	3·9	4·0	3·1
4	14·9	13·1	19·0	159	162	159	68	71	71	5·1	5·2	7·0
5	16·0	13·6	14·6	150	144	153	58	54	56	4·8	5·6	5·5
6	13·7	12·5	14·4	123	126	117	45	39	46	6·2	5·4	5·7
7												
8	13·2	11·9	14·5	141	150	138	42	40	39	4·7	5·8	6·5
9	10·8	11·9	7·4	99	108	90	38	47	25	4·3	5·1	3·5
Mean	13·8	13·3	13·2	132	134	128	55	55	47	4·7	5·2	4·9
SE	0·6	0·5	1·2	7	6	9	14	13	13	0·3	0·3	0·6
p		NS	NS		NS	NS		NS	NS		NS	NS

Pl, placebo; H, hydralazine; Pr, prazosin.

Table 3 *Observations during steady state exercise*

Case no.	*Oxygen uptake (ml/kg per min)*			*Heart rate (b/min)*			*Mean arterial pressure (mmHg)*			*Cardiac index (l/min per m^2)*			*Stroke volume index (ml/m^2)*		
	Pl	*H*	*Pr*	*Pl*	*H*	*Pr*	*Pl*	*H*	*Pr*	*Pl*	*H*	*Pr*	*Pl*	*H*	*Pr*
1	1105	1032	703	108	111	99	88	87	87	3·3	4·1	2·6	31	37	26
2	613	635	680	132	132	141	90	90	90	2·2	3·5	2·9	17	27	22
3	782	871	928	136	123	108	96	85	76	2·7	3·3	2·7	20	27	25
4	1205	1107	1457	150	148	142	110	120	107	4·0	3·9	5·1	27	26	36
5	916	1008	893	147	141	147	93	100	96	4·7	4·4	3·8	32	31	26
6	565	732	659	105	111	102	97	87	87	3·2	3·5	3·4	31	32	33
7	568	476	402	102	105	111	107	117	113	3·0	2·7	3·6	29	26	32
8	1038	880	1109	138	144	135	92	90	86	4·4	4·1	5·1	32	29	38
9	698	769	615	87	102	87	93	110	95	2·6	3·4	2·1	30	34	25
Mean	832	836	827	123	124	119	96	98	93	3·3	3·7	3·4	28	30	29
SE	86	72	110	8	6	8	3	5	4	0·3	0·2	0·4	2	1	2
p		NS	NS		NS	NS		NS	NS		NS	NS		NS	NS

Pl, placebo; H, hydralazine; Pr, prazosin.

workload achieved. Neither hydralazine nor prazosin had any significant effect on the duration of exercise, maximal oxygen uptake, peak heart rate, peak ventilation, or peak blood pressure.

SUBMAXIMAL STEADY STATE EXERCISE
Measurements taken during the fourth minute of steady state exercise, after hydralazine and prazosin, are shown in Table 3. No significant change in heart rate, arterial blood pressure, cardiac index, systemic vascular resistance, arteriovenous oxygen content difference, or lactate production was observed after either vasodilator drug.

Discussion

The patients in the present study all had a severe limitation of their effort tolerance and only achieved a maximal oxygen consumption of 13·8 ml/min per kg. This probably resulted from the restricted rise in cardiac output as well as the rise in the pulmonary venous pressures. Vasodilator drugs, if effective during exertion, might be expected to improve the factors that limit exercise performance. Hydralazine, an arteriolar vasodilator when given to resting supine patients with cardiac failure, increases the cardiac output, yet has only a modest effect on pulmonary venous pressures.[2] In contrast, prazosin acts both on the arteriolar resistance and the venous capacitance vessels: at rest, there is an increase in cardiac output and a fall in left ventricular filling pressures.[9] Prazosin might therefore be expected to improve exercise capacity more than hydralazine by virtue of its double site of action. On the other hand, venodilatation may reduce the venous return during exertion and further limit a rise in cardiac output.

Although the predicted beneficial effects of both hydralazine and prazosin occurred at rest, there was no improvement in either maximal effort capacity or cardiac output during submaximal steady state exercise.

The failure of vasodilator drugs to improve the exercise performance of patients with cardiac failure may be the result of an interaction of several mechanisms. In the exercising patient with cardiac failure, the normal reduction of peripheral vascular resistance, and thus afterload, is restricted by increased sympathetic activity[10] as well as an increased stiffness of the walls of the muscular arterioles.[11] In the present study using the doses of drugs administered and the exercise loads studied, there was no augmentation of the fall in systemic vascular resistance towards normal levels by either agent.

The oxygen delivery to exercising muscles is an important factor limiting exercise capacity in both health and disease.[12] In cardiac failure, the inadequate increase in cardiac output,[13] and a limited ability of the resistance vessels in skeletal muscle to dilate,[11] will decrease the oxygen delivery to the active muscle and reduce exercise capacity. Arteriolar vasodilator drugs act predominantly on visceral and skin vessels as well as dilating the arterioles in resting muscle, yet they would be expected to have no effect on the resistance vessels in the muscle of the exercising limb, which are already maximally dilated. Thus, any potentially beneficial increase in cardiac output may be diverted away from the exercising muscle, and could potentially decrease exercise capacity.

The reduction of both left and right ventricular filling pressures with drugs which dilate the systemic and pulmonary venous capacitance vessels, though decreasing pulmonary congestion, may interfere with the reflex venoconstriction which normally increases venous return and maintains the cardiac output during exercise. The present group of

Systemic vascular resistance (dynes s cm^{-5})			*Arteriovenous oxygen content (ml/100 ml)*		
Pl	*H*	*Pr*	*Pl*	*H*	*Pr*
1083	838	1338	17·0	12·4	13·5
2181	1411	1674	18·6	12·4	15·8
1567	986	1240	16·3	14·7	19·3
1202	1333	858	14·9	14·0	14·1
918	1052	1164	11·3	13·2	13·5
1410	1160	1288	10·2	12·2	12·2
1902	2340	1738	12·6	11·9	7·7
898	973	695	12·6	12·0	11·2
1430	1294	1767	13·4	11·3	14·3
1399	1265	1178	14·1	12·6	13·5
145	148	181	0·9	0·4	1·1
	NS	NS		NS	NS

patients had a severely limited exercise capacity despite maximal treatment with diuretics. Further reduction of the effective circulating volume by venodilatation may augment the effect of a diuresis by reducing exercise performance further.[14]

The results of the present study are similar to those observed after nitrates[15] and hydralazine plus nitrates.[6] In both studies, no differences were observed at maximal effort, though during submaximal exertion cardiac output was slightly higher after the drugs. After the short-term oral administration of prazosin, Rubin *et al.*[5] observed no haemodynamic change at rest yet an increased stroke volume and decreased filling pressures during supine exercise. The apparently differing results may be explained both by the supine posture, and a sympatholytic effect which persists after tachyphylaxis to the vasodilator effect of prazosin has developed.[16] The adrenergic blockade may enhance the limited decrease in vascular resistance by overcoming the sympathetic hyperactivity which occurs during exercise in patients with heart failure.[10] The improvement of exercise capacity in patients with chronic rheumatic heart disease after nitrates[4] is probably the result of a reduction in valvular regurgitation, an improvement that persists during exercise.

Finally, it is interesting that though the acute administration of a vasodilator drug has little effect on the peak exercise performance of the patient with cardiac failure, the long-term administration of nitrates,[17] prazosin,[18] and trimazosin[19] does improve exercise capacity. The differences between the effects of a first dose of a vasodilator and those observed after a long period of administration are unclear. An improvement in renal perfusion will increase the response of the kidneys to diuretics and mobilise extravascular fluid. The removal of perivascular oedema will improve the dilator capacity of the muscular arterioles[11] and may then allow the vasodilator drug to augment the limited fall in systemic vascular resistance during exercise. A comparison of the haemodynamic response to exercise after the acute administration and long-term treatment with a vasodilator drug is now desirable to establish why the differences exist.

References

1 Guilia HH, Cohn JM, Mikulic E, Franciosa JA, Limas JC. Treatment of refractory heart failure with infusion of nitroprusside. *N Engl J Med* 1974; **291:** 587–92.

2 Chatterjee K, Parmley WW, Massie B, *et al.* Oral hydralazine therapy for chronic refractory heart failure. *Circulation* 1976; **54:** 879–83.

3 Fitchett DH, Marin Neto JA, Oakley CM, Goodwin JF. Hydralazine in the management of left ventricular failure. *Am J Cardiol* 1979; **44:** 303–9.

4 Borer J, Redwood DR, Itscoitz SB, Goldstein RE, Epstein SE. Nitroglycerin-induced improvement in exercise tolerance and hemodynamics in patients with chronic rheumatic heart valve disease. *Am J Cardiol* 1978; **41:** 302–7.

5 Rubin SA, Chatterjee K, Gelberg HJ, Ports TA, Brundage BH, Parmley WW. Paradox of improved exercise but not resting hemodynamics with short-term prazosin in chronic heart failure. *Am J Cardiol* 1979; **43:** 810–5.

6 Franciosa JA, Cohn JN. Immediate effects of hydralazine-isosorbide dinitrate combination on exercise capacity and exercise hemodynamics in patients with left ventricular failure. *Circulation* 1979; **59:** 1085–91.

7 Ferguson RJ, Faulkner JA, Julius S, Conway T. Comparison of cardiac output determined by CO_2 rebreathing and dye dilution methods. *J Appl Physiol* 1960, **25:** 450–4.

8 Franciosa JA, Ragan DO, Rubenstone A. Validation of the CO_2 rebreathing method for measuring cardiac output in patients with hypertension or heart failure. *J Lab Clin Med* 1976; **88:** 672–82.

9 Miller RR, Awan NA, Maxwell KS, Mason DT. Sustained reduction of cardiac impedance and preload in congestive heart failure with the antihypertensive vasodilator Prazosin. *N Engl J Med* 1977; **297:** 303–7.

10 Chidsey CA, Harrison DC, Braunwald E. Augmentation of the plasma nor-epinephrine response to exercise in patients with congestive heart failure. *N Engl J Med* 1962; **267:** 650–4.

11 Zelis R, Mason DT, Braunwald E. A comparison of the effects of vasodilator stimuli on peripheral resistance vessels in normal subjects and in patients with congestive heart failure. *J Clin Invest* 1968; **47:** 960–70.

12 Shepherd J, VanHoutte P. Skeletal muscle blood flow: neurogenic determinants. In: Zelis R, ed. *The peripheral circulations.* New York: Grune & Stratton, 1975: 3–55.

13 Wade OL, Bishop JM. *Cardiac output and regional blood flow.* Oxford: Blackwell Scientific, 1962.

14 Epstein SE, Beiser GD, Stampfer M, Braunwald E. Depression of cardiac output at rest and during exercise produced by diuresis in patients with cardiac decompensation (abstract). *Clin Res* 1967; **15:** 200.

15 Franciosa JA, Cohn JN. Effects of isosorbide dinitrite on response to submaximal and maximal exercise in patients with congestive heart failure. *Am J Cardiol* 1979; **43:** 1009–14.

16 Arnold S, Williams R, Ports T, Baughman R, Benet L, Chatterjee K. Prazosin kinetics and effect in congestive heart failure (abstract). *Am J Cardiol* 1979; **43:** 403.

17 Franciosa JA, Nordstrom LA, Cohn JN. Nitrate therapy for congestive heart failure. *JAMA* 1978; **240:** 443–6.

18 Awan NA, Miller RR, DeMaria A, Maxwell KS, Neumann A, Mason DT. Efficacy of ambulatory vasodilator therapy with oral prazosin in chronic refractory heart failure. *Circulation* 1977; **56:** 346–54.

19 Aronow WS, Greenfield RS, Alimadadian H, Danahy DT. Effect of the vasodilator trimazosin versus placebo on exercise performance in chronic left ventricular failure. *Am J Cardiol* 1977; **40:** 789–93.

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Postural heart block*

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SUMMARY A patient presented with orthostatic dizziness and syncope caused by postural heart block. When the patient was supine, atrioventricular conduction was normal and he was asymptomatic; when he was standing he developed second degree type II block and symptoms. The left bundle-branch block on his electrocardiogram and intracardiac electrophysiological study findings suggest that this heart block occurred distal to the His bundle.

Orthostatic symptoms are usually presumed to be secondary to an inappropriate distribution of intravascular volume or to autonomic nervous system abnormalities. As shown in this patient, these symptoms may be the result of orthostatic heart block. Ambulatory monitoring may be useful in patients with orthostatic neurological symptoms, particularly when conduction abnormalities are present on the electrocardiogram.

Orthostatic neurological symptoms usually result from inadequate cerebral perfusion caused by disturbances of the autonomic nervous system,[1-3] ineffective or inappropriate shifts in volume distribution,[4] or drugs.[5] We report a patient with orthostatic dizziness and syncope caused by intermittent postural heart block.

Case report

A 53-year-old truck driver was asymptomatic until February 1976 when he experienced dizziness and syncope after standing. In the next 18 months he experienced three more episodes of syncope and many of dizziness. *All* occurred when he changed from a sitting or supine to a standing position. Neurological examination, an electroencephalogram, and a brain scan were normal. An electrocardiogram revealed left bundle-branch block and a prolonged PR interval. Twenty-four hour ambulatory monitoring and a treadmill exercise test were unremarkable. He was referred to the University of Oregon Health Sciences Center in October 1977 for further evaluation.

On examination, the supine blood pressure was 140/70 mmHg and the upright pressure was 125/70 mmHg. The pulse rate when supine was 80 beats a minute and regular, and increased to 90 beats a minute with some irregularity when he was upright. The carotid pulse was normal, and there were no carotid bruits. The cardiac impulse was normal. The second heart sound was paradoxically split. There was a grade 2/6 apical systolic murmur. These findings did not change when the patient changed from the supine to the standing position. The remainder of the physical examination was normal. An electrocardiogram disclosed left bundle-branch block with a PR interval of 0·21 second. Chest *x*-ray film was normal. An echocardiogram disclosed left atrial enlargement. All blood tests performed including the glucose level were normal.

On numerous occasions the patient's pulse rate fell with standing, and each time he felt dizzy. Because of the pulse changes, a continuous electrocardiographic rhythm strip was taken during the change of position (Fig. 1). When supine, the patient had a regular sinus rhythm at 100 beats a minute; when he stood up, he was again dizzy and intermittent type II second-degree atrioventricular block was seen. After resuming a supine position he returned to normal sinus rhythm at a rate of 100 beats a minute. Carotid sinus massage resulted in sinus arrest with two second pauses but no symptoms.

His bundle electrocardiography was performed the following day. At the start of the study the patient was in normal sinus rhythm. When a

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number 7 French tripolar His bundle recording catheter was advanced across the tricuspid valve into the right ventricle, the patient developed complete heart block below the His bundle (Fig. 2); the ventricular escape rate was 24 beats a minute. The patient felt dizzy but was alert and able to speak. The third degree heart block was not abolished by the intravenous injection of 1 mg atropine or by withdrawal of the wire from the right ventricle. The wire was then advanced into the right ventricle and ventricular pacing was established; the patient became pacemaker dependent. Subsequently, he returned to sinus rhythm with first degree atrioventricular block. His bundle recordings showed normal PA and AH intervals but the HV interval was much prolonged (116 ms, normal $\leqslant$55 ms).[6] His bundle recordings could not be obtained during standing because of his condition. A permanent pacemaker was implanted and after 14 months the patient remains completely free from his previous symptoms.

Discussion

The orthostatic symptoms in this patient were caused by the development of high degree atrioventricular block when he assumed the upright position. This is the first case that we are aware of where heart block was shown to be orthostatic. Though postural symptoms are most commonly secondary to volume or autonomic nervous system abnormalities (which may be caused by micturition, swallowing, coughing, and hiccoughing),[5] changes in conduction should now also be considered.

There are a number of features that suggest that the type II block occurred distal to the His bundle. The initial electrocardiogram showed left bundle-branch block. The patient developed type II block which usually occurs below the His bundle,[7] particularly in the absence of digitalis toxicity or congenital cardiac defects. The HV interval was greatly prolonged and the site of heart block was shown to be below the His bundle. The latter cannot be related directly to his presentation because induction of the right bundle-branch block by a catheter in the right heart[8] in this patient with left bundle-branch block could have been the cause of the complete heart block. This rhythm could not be precipitated by carotid sinus massage nor, when present, did it respond to the administration of atropine; both suggest that the block was more likely to have occurred in the distal conduction system.[5] Though complete heart block below the His bundle has been reported secondary to carotid sinus massage suggesting some vagal or sympathetic

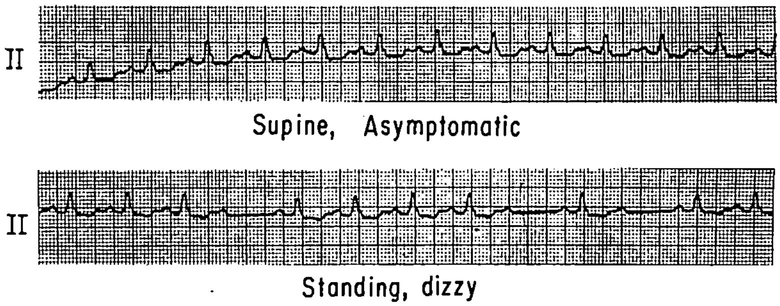

Fig. 1 *When supine the patient was asymptomatic and in sinus rhythm at the rate of 100 beats a minute* (top strip): *when he stood, intermittent type II second degree atrioventricular block developed* (bottom strip) *and he was dizzy. Paper speed 25 mm/s.*

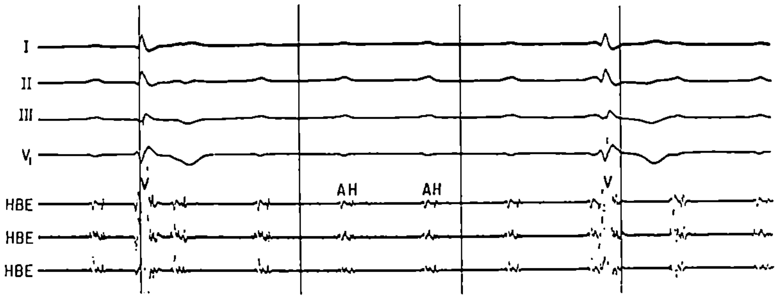

Fig. 2 *His bundle tracings taken as the recording catheter was passed into the right ventricle shows complete heart block below H with a ventricular (V) escape rate of 24 beats/min. Leads I, II, II, and V1, from the surface electrocardiogram, and three His bundle leads (HBE) are shown.* A *is the atrial depolarisation and* H *is the His bundle depolarisation. Paper speed 100 mm/s.*

withdrawal effects on distal Purkinje conduction,[9] this is unusual.[10]

Our patient demonstrates that orthostatic neurological symptoms may be secondary to postural heart block. He did not have symptoms with all changes in posture, which is probably why 24-hour electrocardiographic monitoring failed to provide the answer. In a patient with orthostatic symptoms, however, a determined effort should be made to obtain ambulatory electrocardiograms, especially in patients with electrocardiographic evidence of conduction disease.

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References

[1]Shy GM, Drager GA. A neurological syndrome associated with orthostatic hypotension: a clinical-pathologic study. *Arch Neurol* 1960; **2:** 511–27.

[2]Hickler RB. Orthostatic hypotension and syncope (editorial). *N Engl J Med* 1977; **296:** 336–7.

[3]Ziegler MG, Lake CR, Kopin IJ. The sympathetic-nervous-system-defect in primary orthostatic hypotension. *N Engl J Med* 1977; **296:** 293–7.

[4]Ibrahim MM, Taraz RC, Dustan HP, Brano EL. Idiopathic orthostatic hypotension: circulatory dynamics in chronic autonomic insufficiency. *Am J Cardiol* 1974; **34:** 288–94.

[5]Freidberg CK. Syncope: pathological physiology: differential diagnosis and treatment. *Mod Concepts Cardiovasc Dis* 1971; **40:** 55–60.

[6]Dhingra RC, Rosen KM, Rahimtoola S. Normal conduction intervals and responses in 61 patients using His bundle recording and atrial pacing. *Chest* 1973; **64:** 55–9.

[7]Langendorf R, Pick A. Atrioventricular block, type II (Mobitz) — Its nature and clinical significance (editorial). *Circulation* 1968; **38:** 819–21.

[8]Luck JC, Engel TR. Transient right bundle branch block with 'Swan-Ganz' catheterization. *Am Heart J* 1976; **92:** 263–4.

[9]Jonas EA, Kosowsky BP, Ramaswamy K. Complete His-Purkinje block produced by carotid sinus massage. *Circulation* 1974; **50:** 192–7.

[10]Dhingra RC, Denes P, Wu D, Chuquimia R, Roson KM. The significance of second degree atrioventricular block and bundle branch block. Observations regarding site and type of block. *Circulation* 1974; **49:** 638–46.

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Rhabdomyoma of the heart in a newborn infant
Diagnosis by echocardiography

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SUMMARY An intracavitary right ventricular tumour was identified echocardiographically before operation in an infant with a rhabdomyoma of the heart. Necropsy showed associated tuberous sclerosis.

Cardiac tumours occur very rarely in infancy. When present, the commonest of these are rhabdomyomata.[1] Until now, only a few cases of rhabdomyoma have been diagnosed echocardiographically.[2-4] Affected infants with severe involvement usually die as a result of obstruction to blood flow, and thus operation may be undertaken in an attempt at palliation. Tuberous sclerosis is often associated with rhabdomyoma and must be sought.

We are reporting here an infant presenting with right ventricular outflow obstruction caused by rhabdomyoma which was diagnosed by echocardiogram in the first instance. In addition to a discussion of the echocardiographic diagnosis, we also draw attention to the accompanying conduction disturbance, the angiocardiographic features, and the pathology, including the ultrastructure of this tumour.

Case report

This infant girl was born at term by elective caesarean section. A hydatidiform mole had been removed from the mother four months before conception on this occasion. During the first three months of pregnancy she was taking dihydroprogesterone. The parents and two sibs were otherwise normal. There was no history of any fits, rashes, or mental retardation in the family. Birthweight was 2920 g. On the second day of life the infant had a cyanotic spell which responded to oxygen. Duskiness was observed at times during the next few days and because further cyanotic attacks occurred, she was referred to the Transvaal Memorial Hospital for Children for assessment. Abnormal physical findings at 9 days of age, apart from a right hip click, were confined to the cardiovascular system. She was moderately cyanosed at rest. The pulses were normal and the heart rate 140 per minute. A parasternal heave of right ventricular hypertrophy was present. The second heart sound was single and was preceded by a grade 2/6 systolic murmur, heard maximally at the second left interspace. A continuous murmur was audible under the left clavicle. There were no signs of heart failure.

An electrocardiogram showed the features of

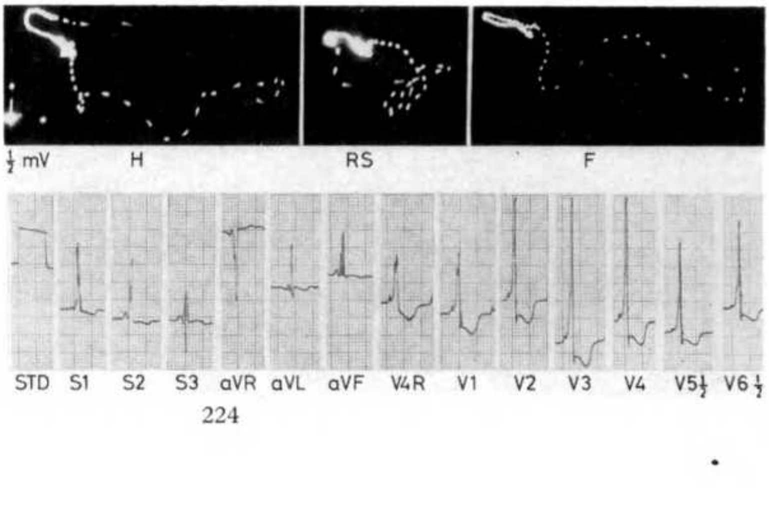

Fig. 1 *Vectorcardiogram* (upper panel) *and electrocardiogram showing type A Wolff-Parkinson-White syndrome.*
H, horizontal; RS, right sagittal; F, frontal.
Note: *Standardisation of electrocardiogram 1 cm = 1 mV (V5 and V6 are half standard).*

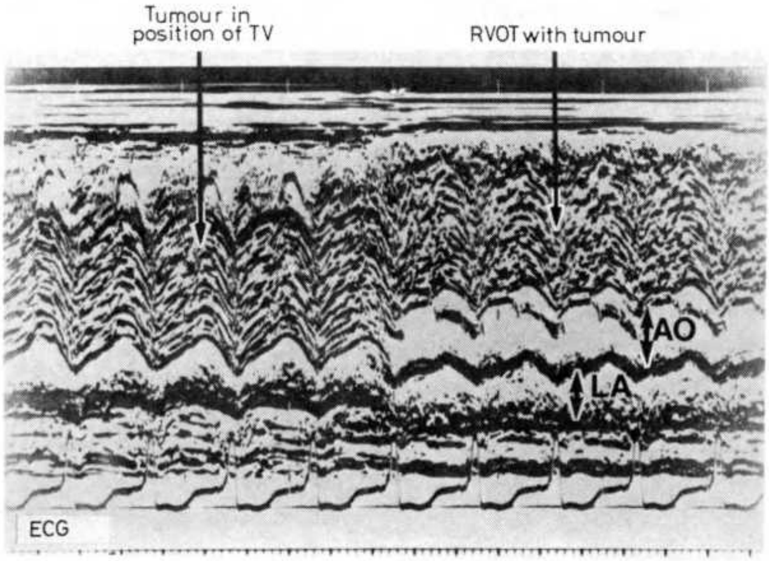

Fig. 2 *Scan from tricuspid valve (TV) to aorta (Ao). Tumour mass is seen within area usually occupied by tricuspid valve, and extends into right ventricular outflow tract (RVOT). Left atrium (LA) is normal in size.*

Wolff-Parkinson-White syndrome type A (Fig. 1). A vectorcardiogram confirmed this diagnosis and showed poor rightward forces (Fig. 1). The chest x-ray film showed normal situs, right atrial enlargement, a pulmonary bay and lung fields that were possibly oligaeic.

A provisional diagnosis of right ventricular outflow obstruction was made. An echocardiogram (Fig. 2) showed a tumour mass which appeared in the area where the tricuspid valve is usually identified, and which extended into the right ventricular outflow tract. The mass was also seen in the right ventricular cavity. The left ventricle and aorta appeared normal. The septum was not clearly seen because of the probable tumour mass.

At cardiac catheterisation, a gradient of 20 mmHg was found across the right ventricular outflow tract. Right-to-left shunting at atrial level was demonstrated on oximetry. Systemic arterial saturation was 75 per cent (Table). On angiocardiography (Fig. 3), a mass was seen to indent the right ventricular outflow tract. Left ventriculography also showed some indentation of the outflow tract from the septum. The aorta was seen to feed pulmonary arteries via a persistent ductus arteriosus.

Table *Cardiac catheterisation findings*

Site		*Pressure (mmHg)*	*O_2 saturation (%)*
SVC			67, 67
IVC			74
RA		$a = 12$ $v = 10$ ($m = 10$)	71, 72
RV	high	55 systolic	64
	apex	75/0–10	
MPA		55/20 (m = 40)	—
PV		—	84, 88
LA		$a = 11$, $v = 11$ ($m = 8$)	—
LV		78/0–10	75

IVC, inferior vena cava; PV, pulmonary vein; LA, left atrium; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

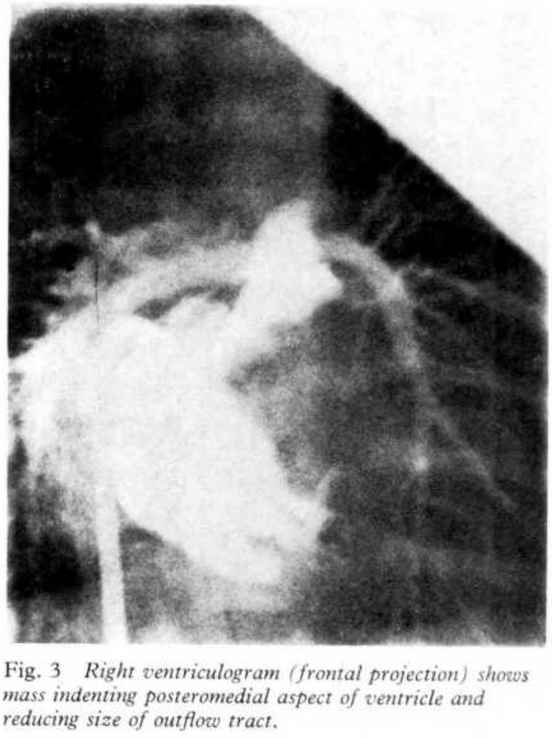

Fig. 3 *Right ventriculogram (frontal projection) shows mass indenting posteromedial aspect of ventricle and reducing size of outflow tract.*

A right atrial injection confirmed shunting from right to left atrium.

At operation the same evening, on opening the right atrium a large white lobulated tumour mass arising from the right ventricle was seen to involve the tricuspid valve and to bulge into the right atrium. It appeared to originate from the ventricular septum. The tumour was removed piecemeal, with resultant destruction of the tricuspid valve mechanism. The foramen ovale was sutured. Surprisingly the infant came off bypass, but succumbed the following day in a low output state with evidence of gross tricuspid regurgitation.

PATHOLOGY

Fragments of tumour tissue removed at operation showed the histological features of a cardiac rhabdomyoma.

NECROPSY

The heart was slightly enlarged and deformed by a bulging tumour mass 3 cm in diameter (Fig. 4) which involved the posterior walls of both atria and extended on to the posterior ventricular surface. Microscopy showed that this crossed the atrioventricular junction near the atrioventricular node. A second tumour 1 cm in diameter involved the apex of the left ventricle. In addition, many other smaller tumours were present throughout the myocardium. On incision of these masses they were white in colour and were clearly demarcated from the rest of the muscle. Histological section (Fig. 4)

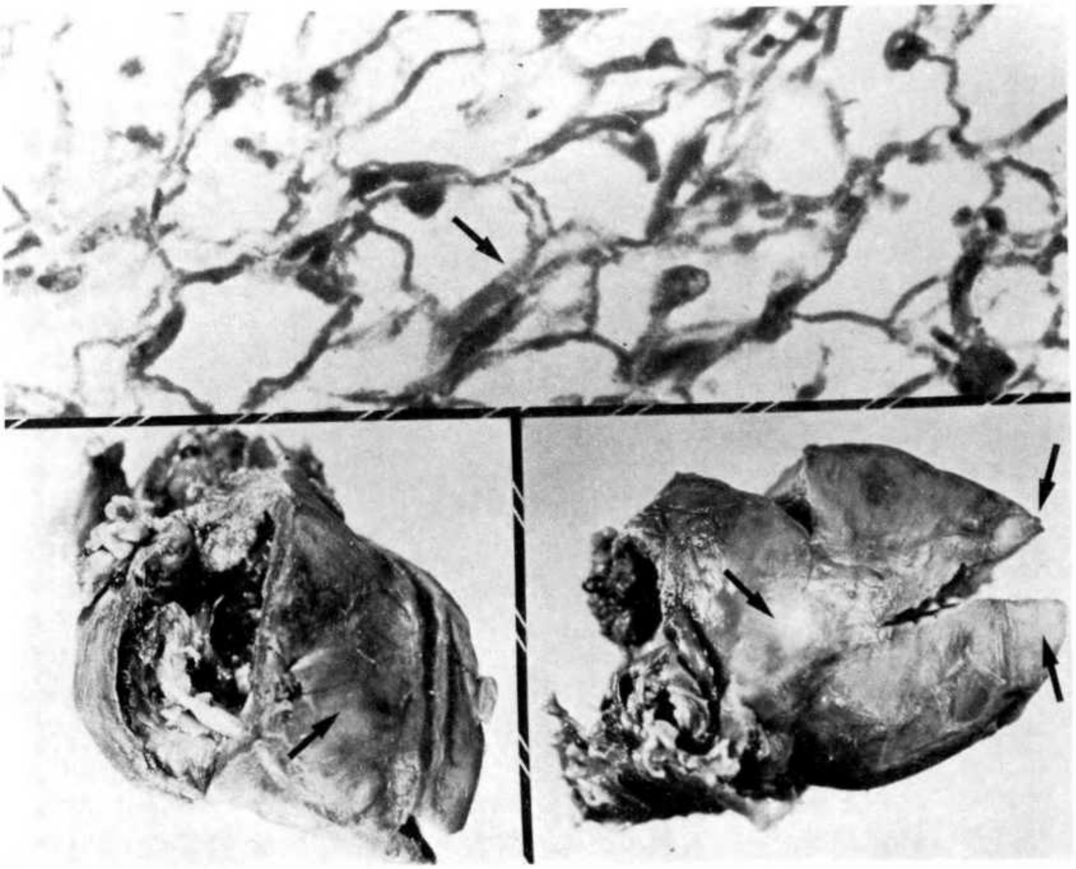

Fig. 4 *Histology of the rhabdomyoma* (upper panel) *showing 'spider cells'. The arrow points to cross-striations seen mainly in the periphery of the cells. Frontal view of the heart* (lower left) *which has a window cut into the right ventricle. The destroyed tricuspid valve is evident. The arrow points to a tumour mass visible on the surface. The right lower panel shows the posterior aspect of the heart. Double arrows indicate tumour at the apex of the heart, while a single arrow points to tumour that was present on the posterior surface of the atria and which was shown by sectioning to cross the atrioventricular groove close to the atrioventricular node.*

showed these areas to consist of discrete masses of large rounded vacuolated cells predominantly with peripherally placed nuclei ('spider cells'). Glycogen was present in the cytoplasm of the 'spider cells' and was concentrated towards the periphery. Cross striations were observed in only a few cells, and when present, were also situated at the periphery of the cells. Electron microscopy showed myofibrils with z-bands, and clusters of leptofibrils with striations at a periodicity of approximately 1600 nm. Glycogen granules were observed in the background.

The brain appeared normal by external appearance, but numerous 'tuberosities' were palpable within the cortex, which on microscopical examination showed diffuse infiltration by large cells with eosinophilic-staining cytoplasm, which were mainly gemistocytic astrocytes, characteristic of tuberous sclerosis.

Apart from the spleen which showed abnormal histiocytes in the red pulp, and the liver, which showed severe portal condensation of collagen containing large abnormal vascular channels, other organs appeared normal.

Discussion

The echocardiographic diagnosis of tumour was easy in this case. Like myxomas, which may have a similar laminar appearance on echocardiography,[5 6] rhabdomyomas appear to be intracavitary but do not prolapse into the ventricle. This patient and other previously reported cases of right ventricular rhabdomyoma[2–4] all showed a static laminar mass related to the ventricular septum and the cavity of the right ventricle.

Other electrocardiographic abnormalities are common, but the Wolff-Parkinson-White syndrome is unusual in patients with rhabdomyomas,[1] though this abnormality was shown in a case illustrated in a standard paediatric cardiology textbook.[7] It appears that a glycogen-containing tumour extending from the atria to the ventricles, as in our case, may conceivably constitute an accessory pathway. Paroxysmal atrial tachycardia did not occur in our infant.

Operation in our case was intended to effect a cure, but as in other cases the tumour was multicentric.[8 9] Palliation may then be all that is possible. Furthermore, many cases have associated tuberous sclerosis and will succumb to the effects of this anomaly.[9] In the absence of a family history, the diagnosis of tuberous sclerosis was not made in our case, until the postmortem examination. Even after death, careful examination of the brain may be necessary to establish the diagnosis. Had our patient survived a successful operation, her prognosis would have been determined by the associated tuberous sclerosis.

We thank Professor R Kinsley and Mr P Colsen who operated on this patient, and the superintendent of the hospital for permission to publish.

References

[1] Nadas AS, Ellison RC. Cardiac tumours in infancy. *Am J Cardiol* 1968; **21:** 363–6.

[2] Allen HD, Blieden LC, Stone FM, Bessinger FB Jr, Lucas RV Jr. Echocardiographic demonstration of a right ventricular tumor in a neonate. *J Pediatr* 1974; **84:** 854–6.

[3] Farooki ZQ, Henry JG, Arciniegas E, Green EW. Ultrasonic pattern of ventricular rhabdomyoma in two infants. *Am J Cardiol* 1974; **34:** 842–4.

[4] Gutgesell HP, Paquet M. *Atlas of Pediatric Echocardiography*. New York: Harper & Row, 1978: 191–4.

[5] Feigenbaum H. *Echocardiography*. Philadelphia: Lea & Febiger, 1972: 155.

[6] Wolfe SB, Popp RL, Feigenbaum H. Diagnosis of atrial tumours by ultrasound. *Circulation* 1969; **39:** 615–22.

[7] Nadas AS, Fyler DC. *Pediatric cardiology*. Philadelphia: WB Saunders, 1972: 282.

[8] Tsakraklides V, Burke B, Mastri A, Runge W, Roe E, Anderson R. Rhabdomyomas of heart. Report of 4 cases. *Am J Dis Child* 1974; **128:** 639–46.

[9] Fenoglio JJ Jr, McAllister HA Jr, Ferrans VJ. Cardiac rhabdomyoma: a clinicopathologic and electron microscopic study. *Am J Cardiol* 1976; **38:** 241–51.

Requests for reprints to Dr Selwyn Milner, Department of Pediatrics, Johannesburg Hospital, Jubilee Road, Parktown, Johannesburg 2193, Republic of South Africa.

Br Heart J 1980; **44**: 228–30

Aneurysm of main left coronary artery

MARK KESSLER, ROBERT I HAMBY, JOSEPH HILSENRATH

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SUMMARY A 57-year-old man presented with exertional chest pain, and was found to have a saccular, lobulated aneurysm of the left main coronary artery associated with severe atherosclerotic vascular disease. This is the third similar case reported and the first case of atherosclerotic origin. All symptoms were relieved by coronary artery bypass surgery.

Angiographic studies have shown that coronary artery aneurysms occur in 1 to 2·5 per cent of patients with coronary artery disease.[1–4] Multiple aetiologies have been reported, most frequently atherosclerotic,[5 6] and/or congenital.[5–7] Other reported causes include bacterial infection,[6] syphilis[6] septic embolism,[7] trauma,[3 8] dissection,[9] polyarteritis nodosa,[10] scleroderma,[11] Ehlers-Danlos syndrome,[12] Marfan's syndrome,[9] metastatic tumour,[7] cystic medionecrosis,[10] and mucocutaneous lymph node syndrome.[13 14]

We describe an aneurysm involving the main left coronary artery; to our knowledge, only three such angiographically documented cases have been previously reported in adults.[15–17]

Case report

This was the first hospital admission for a 57-year-old white man who had been in excellent health until one-and-a-half months before admission. At that time, he developed exertional chest pain associated with dyspnoea and relieved by rest. Because of increasing frequency and duration of this chest pain, in spite of medical treatment, he was admitted for cardiac catheterisation. There was no history of heart disease or hypertension. He had smoked cigarettes for 25 years. Both his father and mother had died of atherosclerotic heart disease at the ages of 65 and 73, respectively. Two brothers died of atherosclerotic heart disease at the ages of 50 and 52, and one sister, age 63, had had a myocardial infarction and was alive.

On physical examination, blood pressure was 120/80 mmHg, and pulse 50 per minute and regular. All peripheral pulses were palpable. No jugular venous distension was noted and carotid upstrokes were normal. Lungs were clear and cardiac examination did not reveal any abnormality. The chest *x*-ray and electrocardiogram were within normal limits. The blood chemistry, including a two-hour postprandial serum glucose were normal. The cholesterol was 4 and triglycerides 1 mmol/l. The cardiac catheterisation was performed with retrograde left ventriculography and selective coronary angiography using Judkins catheters. A left main coronary artery lesion was noted superimposed on severe triple vessel disease. Multiple projections showed a lobulated, septated aneurysm limited to the left main coronary artery (Fig.).

The patient underwent quadruple saphenous vein coronary artery bypass surgery. Two weeks later, a postoperative cardiac catheterisation was performed and all four bypass grafts (left anterior descending, circumflex, intermediate, and posterior descending arteries) were found to be patent and functioning well. The postoperative course was uncomplicated.

Comment

The majority of coronary artery aneurysms have been reported to occur in the right coronary artery, with the circumflex being the next most frequently involved vessel and the left anterior descending artery the most often spared.[1 4 6] To the best of our knowledge, the angiographic diagnosis of a left main coronary artery aneurysm in an adult has been reported three times previously.[15–17] One case[15] involved a young woman (23 years old), who presented with exertional chest pain and a continuous, soft murmur. On catheterisation, she was found to have a saccular aneurysmal dilatation of the left main coronary artery, communicating with another intramuscular aneurysm sac. There were no other associated diseases and this lesion was felt to be congenital. The second case[16] was a 33-year-old woman, who presented with a murmur and was found to have supravalvular aortic stenosis, congenital aneurysm of the left ventricular apex, and aneurysmal dilatation of the main left coronary artery. Her only symptom or associated finding was an embolic cerebral vascular accident. The third case[17] does not give any clinical data. By contrast, the case reported here is of a middle-aged man with a single saccular septated aneurysm of the left main coronary artery associated with atherosclerotic coronary artery disease. No murmurs were present and no symptoms could be attributed to the aneurysm directly. The atherosclerotic vascular disease was sufficiently severe to account for the exertional chest pain that led to his admission. The 23-year-old woman,[15] and the patient presented here underwent coronary bypass, with relief of their symptoms. An earlier report[4] showed no deaths among 30 patients with coronary aneurysm 18 months after coronary bypass surgery. Markis and associates[3] reported a 15 per cent annual mortality in a two-year follow-up of 20 patients treated medically. Several children have been reported with aneurysms of the left main coronary artery associated with mucocutaneous lymph node syndrome, a disease which seems to have a predilection for the main coronary arteries.[13 14]

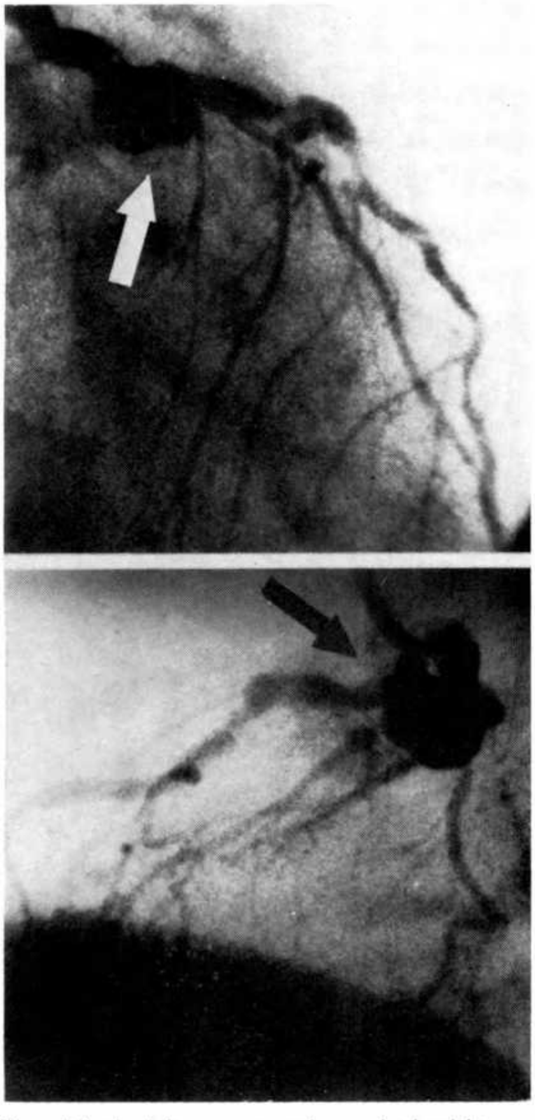

Fig. *Selective left coronary angiogram in the right anterior oblique* (upper) *and left anterior oblique* (lower) *projections showing an aneurysm* (arrow) *of the main left coronary artery just proximal to its bifurcation.*

When examined histologically, weakening of the media was noted as a major cause of arterial dilatation leading to an aneurysm and/or ectasia.[1 18 19] Swanton *et al.*[1] showed severe atherosclerotic involvement with extensive intimal fibrosis leading to weakening of the media in a case of coronary ectasia with atherosclerotic heart disease. Imahori *et al.*[18] showed mucopolysaccharide deposition with intimal sclerosis in the media in Ehlers-Danlos syndrome. Medial involvement in syphilis, polyarteritis nodosa, Marfan's syndrome, and cystic medionecrosis has been well documented.[20] This weakening of the vessel media can easily be recognised as an aetiological factor leading to arterial dilatation.

The present case of a main left coronary artery aneurysm of probable atherosclerotic origin in an adult is, to our knowledge, the first to be reported.

References

1 Swanton RH, Lea Thomas M, Jenkins BS, Webb-Peploe MM, Williams BT. Coronary artery ectasia—a variant occlusive coronary arteriosclerosis. *Br Heart J* 1978; **40:** 393–400.
2 Befeler B, Aranda JM, Embi A, Mullin FL, El-Sherif N, Lassara R. Coronary artery aneurysms. *Am J Med* 1977; **62:** 597–607.
3 Markis JE, Joffe CD, Cohn PF, Feen DJ, Herman MV, Gorlin R. Clinical significance of coronary arterial ectasia. *Am J Cardiol* 1976; **37:** 217–22.

4 Aintablian A, Hamby RI, Hoffman I, Kramer RJ. Coronary ectasia: incidence and results of coronary bypass surgery. *Am Heart J* 1978; **96:** 309–15.

5 Björk L. Ectasia of coronary arteries. *Radiology* 1966; **87:** 33–4.

6 Daoud AS, Pankin D, Tulgan H, Florentin RA. Aneurysms of the coronary artery: report of ten cases and review of literature. *Am J Cardiol* 1963; **11:** 228–37.

7 Crocker DW, Sobin S, Thernas WC. Aneurysms of the coronary arteries: report of three cases in infants and review of the literature. *Am J Pathol* 1957; **33:** 819–37.

8 Konecke LL, Spitzer S, Mason D, Kasparian H, James PM. Traumatic aneurysm of the left coronary artery. *Am J Cardiol* 1971; **27:** 221–3.

9 McKeown F. Dissecting aneurysm of the coronary artery in arachnodactyly. *Br Heart J* 1960; **22:** 434–6.

10 Boschetti AE, Levine A. Cystic medionecrosis with dissecting aneurysm of coronary arteries. *Arch Intern Med* 1958; **102:** 562–70.

11 Chaithiraphan S, Goldberg E, O'Reilly M, Jootar P. Multiple aneurysms of coronary artery in sclerodermal heart disease. *Angiology* 1973; **24:** 86–93.

12 Shiro I, Bannerman RM, Graf CJ, Brennan JC. Ehler's-Danlos syndrome with multiple arterial lesions. *Am J Med* 1969; **47:** 967–77.

13 Yoshikawa J, Yanagihara K, Owaki T, *et al.* Cross-sectional echocardiographic diagnosis of coronary artery aneurysms in patients with the mucocutaneous lymph node syndrome. *Circulation* 1979; **59:** 133–9.

14 Kato H, Koike S, Yamamoto M, Ito Y, Yano E. Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome. *J Pediatr* 1975; **80:** 892–8.

15 Seabra-Gomes R, Somerville J, Ross DN, Emanuel R, Parker DJ, Wong M. Congenital coronary artery aneurysms. *Br Heart J* 1974; **36:** 329–35.

16 Gupta MP, Zoneraich S, Aintablian A, Mehta J. Congenital aneurysm of the left ventricle associated with supravalvular aortic stenosis and aneurysm of the left main coronary artery. Case report and review of the literature. *Angiology* 1975; **26:** 269–75.

17 Weyman AE, Feigenbaum H, Dillon JC, Johnston KW, Eggleton RC. Noninvasive visualization of the left main coronary artery by cross-sectional echocardiography. *Circulation* 1976; **54:** 169–74.

18 Imahori S, Bannerman RM, Graf CJ, Brennan JC. Ehler's-Danlos syndrome with multiple arterial lesions. *Am J Med* 1969; **47:** 967–77.

19 Hudson REB. *Cardiovascular pathology.* London: Edward Arnold, 1965.

20 Robbins SL. *Pathologic basis of disease.* Philadelphia, London, Toronto: WB Saunders, 1974.

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Correspondence

Br Heart J 1980; **44:** 231

Echocardiographic criteria for Ebstein's anomaly of tricuspid valve

Sir,

I read with interest the paper by Gussenhoven and her colleagues[1] on the echocardiographic critiëria for Ebstein's anomaly of the tricuspid valve. I agree with their main conclusion that cross-sectional echocardiography is better than M-mode echocardiography for making this diagnosis. I am however puzzled by their finding of late tricuspid closure (later than mitral closure by 65 ms or more) in eight out of 20 patients with right ventricular volume overload for reasons other than Ebstein's anomaly, mainly with atrial septal defect. This does not agree with my experience. To verify this I looked at the preoperative echocardiographic records of the last 20 consecutive patients operated on at our institution for secundum atrial septal defects. In none of them did I find that tricuspid valve closure occurred later than 60 ms after mitral valve closure. The discrepancy between our findings presumably results from the different ages of the patients. The group of patients with right ventricular volume overload reported by Dr Gussenhoven and her colleagues[1] ranged in age from 21 to 66 (mean 38) whereas our patients were all less than 19 years of age (mean 8). In my opinion the demonstration of greatly delayed tricuspid valve closure (65 ms or more later than that of the mitral valve) in a child, gives rise to strong suspicion of the diagnosis of Ebstein's anomaly of the tricuspid valve. Cross-sectional echocardiography can however demonstrate the displaced septal tricuspid leaflet, the size of the atrialised portion of the right ventricle as well as the size of the functional right ventricle, which is extremely important in making the diagnosis and planning the surgical treatment of this disorder.

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S-221 85 Lund, Sweden.

Reference

1 Gussenhoven WJ, Spitaels SEC, Bom N, Becker AE. Echocardiographic criteria for Ebstein's anomaly of tricuspid valve. *Br Heart J* 1980; **43:** 31–7.

This letter was shown to Dr Gussenhoven and her colleagues who reply as follows:

Sir:

Like Dr Lundström we also were surprised by the finding that delayed tricuspid valve closure of more than 65 ms could occur for reasons other than Ebstein's anomaly. Whether this discrepancy could relate to a difference in age between his patients and ours, as suggested by Dr Lundström, is of interest and needs further evaluation.

Since the preparation of our paper we have examined another 10 patients with proven Ebstein's anomaly. Two of these showed a delay of less than 65 ms, being 0 and 20 ms, respectively. These findings further underline the fact that the valve anatomy of Ebstein's anomaly is variable and thus can account for a wide range in the gap between mitral and tricuspid closure.

Like Dr Lundström we still consider delayed tricuspid valve closure of more than 65 ms suspicious for Ebstein's anomaly, but we have shown its shortcomings as a diagnostic point. It is for this reason in particular that we advocate positive identification of the hallmark of the anomaly, that is distal displacement of the septal attachment of the tricuspid valve leaflet, for which cross-sectional echocardiography is most appropriate.

W J Gussenhoven,
S E C Spitaels,
N Bom,
A E Becker.

Notices

Br Heart J 1980; **44:** 232

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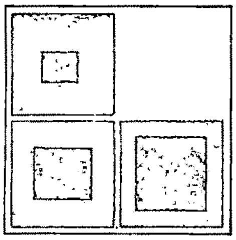

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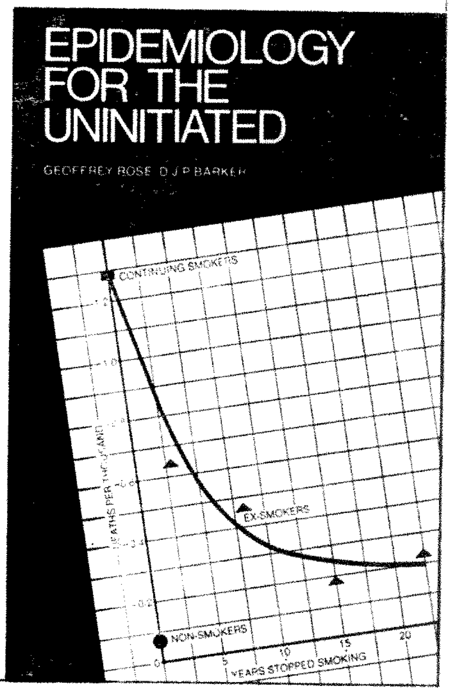

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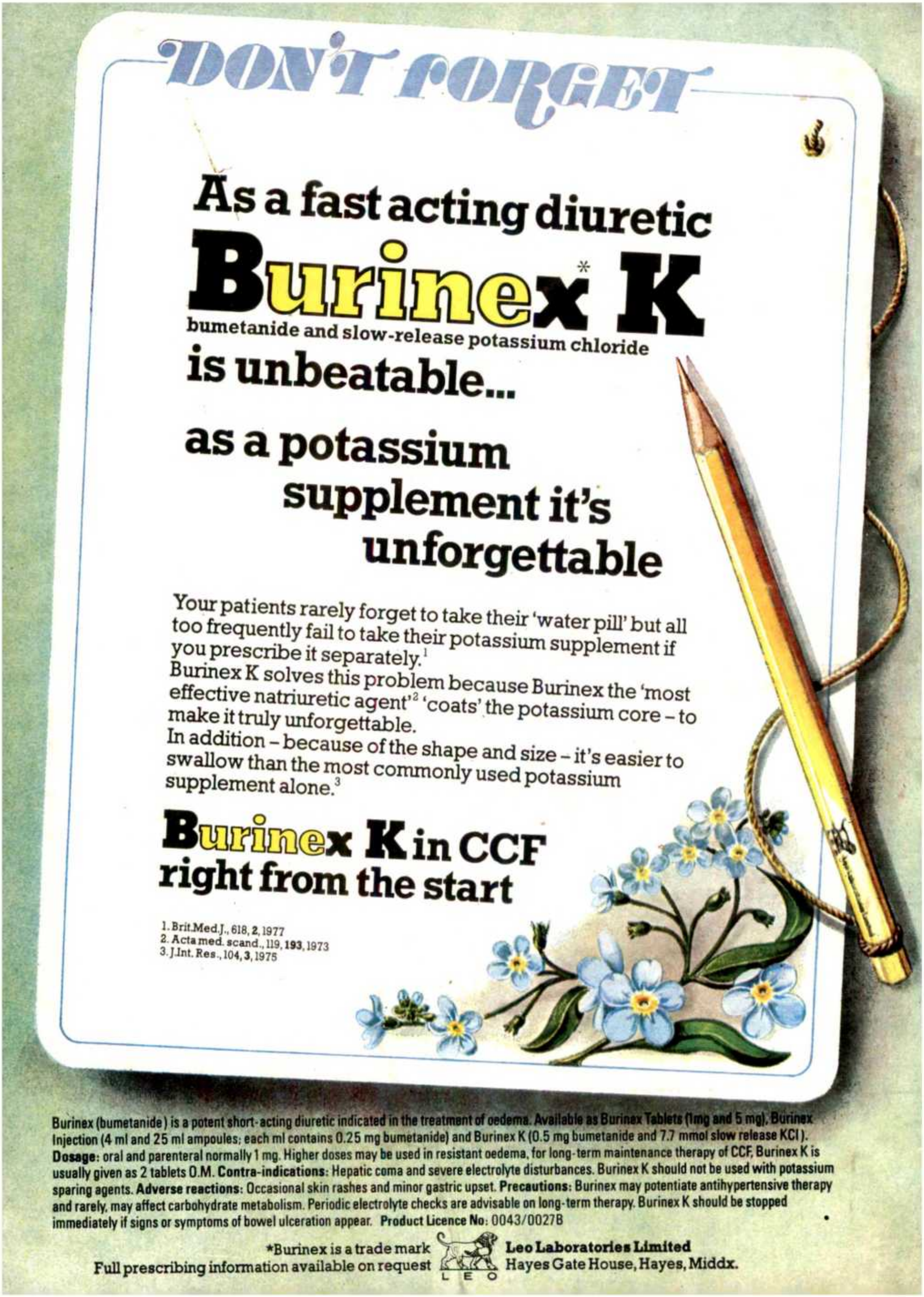

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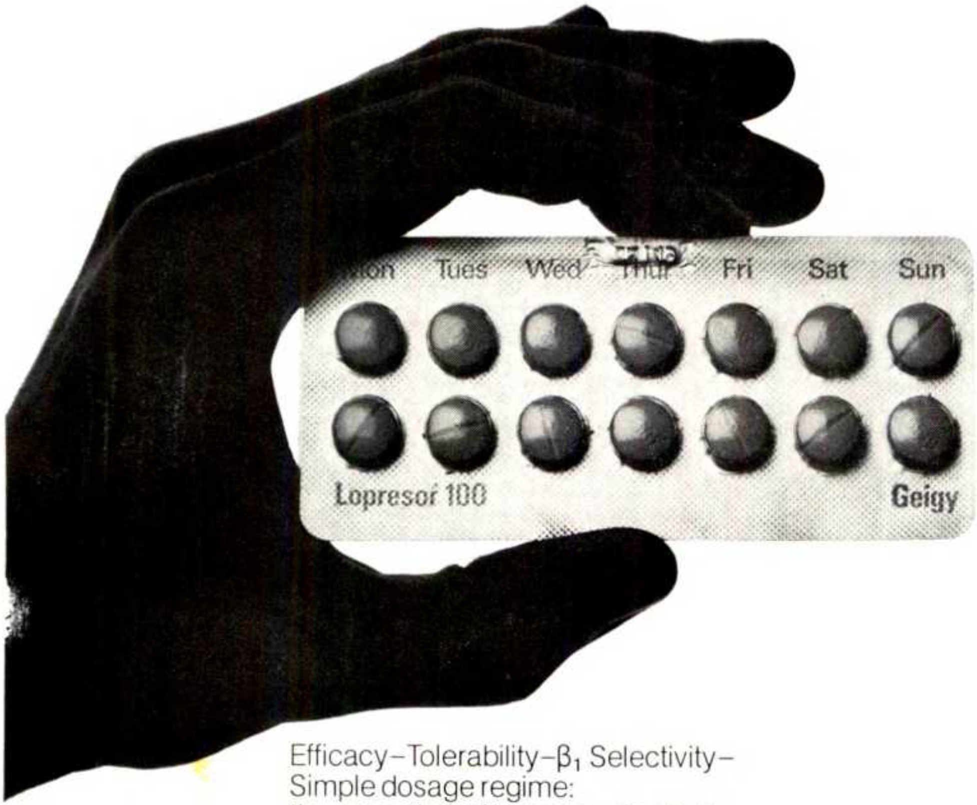

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Heart rate and ectopic prematurity in relation to sustained ventricular arrhythmias*

SALIM YUSUF, ROBERTO LOPEZ, PETER SLEIGHT

From the Department of Cardiovascular Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford

SUMMARY Forty-four patients with acute myocardial infarction were studied using 24-hour electrocardiographic monitoring. A linear correlation has been shown to exist between heart rate preceding accelerated idioventricular rhythm and ventricular tachycardia and the rates of these. The prematurity index was found to be inversely related to the preceding heart rate and also to the rate of accelerated idioventricular rhythm or ventricular tachycardia. Faster heart rates preceded extrasystoles with shorter prematurity indices and a significant inverse correlation was observed between preceding heart rate and prematurity index. Patients developing ventricular tachycardia had more frequent isolated ventricular extrasystoles and faster heart rates preceding the episode as compared with patients not showing ventricular tachycardia. No association was observed between ventricular tachycardia and accelerated idioventricular rhythm. All four patients developing ventricular fibrillation showed preceding ventricular tachycardia, with three of these patients demonstrating faster rates of ventricular tachycardia (>170/min) and shorter prematurity indices (<0·80) than patients without ventricular fibrillation.

Heart rate may influence the severity of ventricular arrhythmia; the prematurity of an extrasystole is of importance in patients developing accelered idioventricular rhythm or ventricular tachycardia.

In an attempt to define rhythms predictive of ventricular fibrillation and ventricular tachycardia, several workers have identified "warning arrhythmias". The early ventricular extrasystole interrupting the T wave has long been considered to be hazardous and a precursor of ventricular fibrillation.[1–3] In patients with acute myocardial infarction, antiarrhythmic therapy has been instituted when R on T extrasystoles have been identified.[4] However, recent reports have challenged this view.[5 6] Other reports suggest that faster heart rates, frequent isolated ventricular extrasystoles, and couplets predispose to ventricular tachycardia and ventricular fibrillation.[2 7] However, the relation of the preceding heart rate to the prematurity of an extrasystole (prematurity index = coupling interval between preceding sinus complex and the first extrasystole/QT interval of the preceding sinus complex); and the relation of the prematurity index to the rate of the following ventricular arrhythmia has not been studied in patients with myocardial infarction.

The purpose of this study was to investigate the following:

(i) The relation of the mean heart rate and the heart rate preceding a run of ventricular arrhythmia to the incidence and the rate of the ventricular arrhythmia and to the prematurity of the extrasystole starting the ventricular arrhythmia.

(ii) The relation between the prematurity index and the rate and incidence of ventricular tachycardia and accelerated idioventricular rhythm.

(iii) The association of a particular ventricular arrhythmia to other types of arrhythmia.

Methods

Forty-four patients admitted to the coronary care unit of the Radcliffe Infirmary with both electrocardiographic (recent ST segment elevation and Q wave development) and enzyme evidence (at least twice normal values of creatine kinase) of acute myocardial infarction were studied at a mean time of six hours after the onset of chest pain. Thirty patients were studied within six hours, 11 between six and 12 hours, and three between 12 and 18 hours after the onset of chest pain. Twenty-four of these

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patients had anterior infarction and 20 had inferior infarction. The routine management was unaltered by the study procedure; diuretics, digoxin, and antiarrhythmic drugs were administered as indicated. A total of eight patients received lignocaine (100 mg as a bolus followed by an infusion of 4 mg/min for the first two hours, 3 mg/min for the next two hours, and then 2 mg/min for a period of 20 hours) as antiarrhythmic therapy when ventricular fibrillation or frequent runs of ventricular tachycardia were observed by the nursing staff. Five patients at entry were already on beta-adrenergic blocking drugs for treatment of angina pectoris or hypertension. Nine patients received oral atenolol 100 mg once daily as they were part of a prospective trial of beta-adrenergic blockade. No patient received beta-adrenergic blockers as antiarrhythmic therapy. Of the eight patients on lignocaine, five were also on beta-blockers so that 17/44 were on lignocaine or beta-blockers.

All patients had normal serum levels of potassium and calcium throughout the entire study period.

DETECTION OF VENTRICULAR ARRHYTHMIAS

In all patients we made continuous recordings of the electrocardiogram on the Oxford Instruments Medilog tape-recorder for the first 48 hours after admission. The records were then analysed on an Oxford Instruments Medilog electrocardiograph analysis system at 60 times real time. An observer always checked that the signals counted by the analysis system were accurate. In addition, the tape was then reanalysed by visual counting by the observer. Hourly counts of heart rate, isolated ventricular extrasystoles, couplets (two consecutive ventricular extrasystoles), triplets (three consecutive ventricular extrasystoles), episodes of accelerated idioventricular rhythm (>3 consecutive ventricular extrasystoles at a rate less than 120 beats/min), and ventricular tachycardia (>3 consecutive ventricular complexes at a rate >120/min) were recorded. Ventricular fibrillation occurred in only four of the 44 patients.

In most patients all isolated ventricular extrasystoles were recorded on paper. In a few patients with hourly rates of ventricular extrasystoles >50/hour, sample recordings of ventricular extrasystoles during this period were obtained. In addition, all couplets, triplets, episodes of accelerated idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation were recorded on paper. In cases of sustained accelerated idioventricular rhythm or ventricular tachycardia, the beginning and the end of the arrhythmia were recorded. These recordings were then analysed to ascertain:

(1) The prematurity index of the ventricular extrasystoles, couplets, triplets, accelerated idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation.

(2) The heart rate preceding runs of accelerated idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation from five consecutive sinus complexes.

(3) Rates of accelerated idioventricular rhythm and ventricular tachycardia.

STATISTICAL METHODS

Standard methods of correlation and regression, and paired and unpaired t tests were used. All data are expressed as mean ±1 standard deviation.

Results

(A) HEART RATE

(i) *Variation over 24 hours* (Fig. 1)

A significant positive correlation was observed between the standard deviation and the mean of the individual hourly heart rates over the first 24 hours ($r=0\cdot507$; $p<0\cdot001$) indicating greater variability in patients with higher heart rates.

(ii) *Comparison between anterior and inferior infarcts*

Although the mean heart rate in patients with anterior infarction tended to be higher (73·89 ±18·94) as compared with 67·58 ±13·36 in patients with inferior infarction, this did not reach statistical significance ($p>0\cdot05$).

(iii) *Relation of mean heart rate to ventricular arrhythmias*

The mean heart rate averaged over 24 hours in

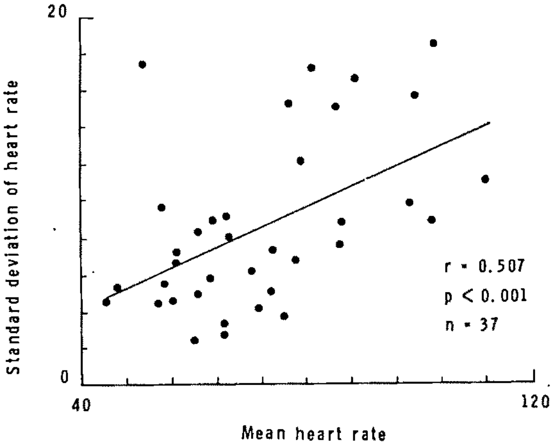

Fig. 1 *Relation of the mean heart rate to the variation in heart rate.*

patients with ventricular tachycardia was not significantly different from those without ventricular tachycardia. Mean heart rate in patients with only accelerated idioventricular rate was 63 ±11·36 as compared with 69 ±12·70 in patients with accelerated idioventricular rate and ventricular tachycardia and 82·83 ±33·15 in patients showing ventricular tachycardia alone. This trend, however, did not reach statistical significance.

(iv) *Relation of preceding heart rate to rate of ventricular arrhythmias*

A significant positive correlation between preceding heart rate and the rate of the accelerated idioventricular rate or ventricular tachycardia was observed when compared as continuous variables ($r=0{\cdot}491$; $p<0{\cdot}001$). This relation was even more significant when accelerated idioventricular rate was considered separately ($r=0{\cdot}696$; $p<0{\cdot}001$; $n=52$) (Fig. 2). In contrast, no significant relation between preceding sinus rate and the rate of ventricular tachycardia was observed ($r=0{\cdot}295$, $n=34$) (Fig. 3). However, the heart rate preceding ventricular tachycardia was faster (78·92 ±21·83) compared with the heart rate preceding accelerated idioventricular rate (67·79 ±18·01) ($2p<0{\cdot}02$; unpaired "t" test; Fig. 4).

(v) *Relation of preceding heart rate to prematurity index* (Fig. 5)

A significant inverse correlation between the heart rate preceding accelerated idioventricular rate and ventricular tachycardia and the prematurity index of the first ventricular extrasystole was observed ($r=-0{\cdot}525$; $p<0{\cdot}001$, $n=70$).

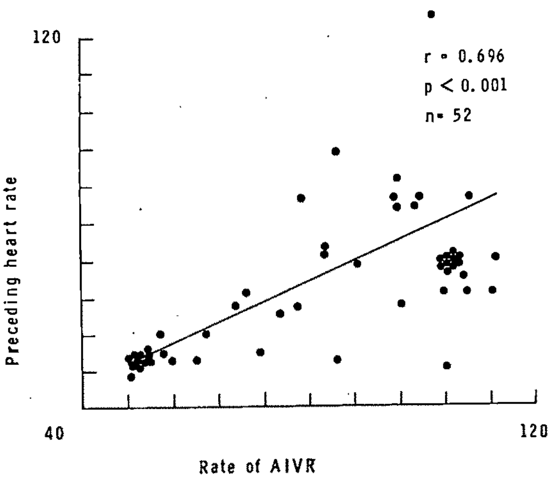

Fig. 2 *Relation of the preceding heart rate to the rate of idioventricular rhythm (AIVR).*

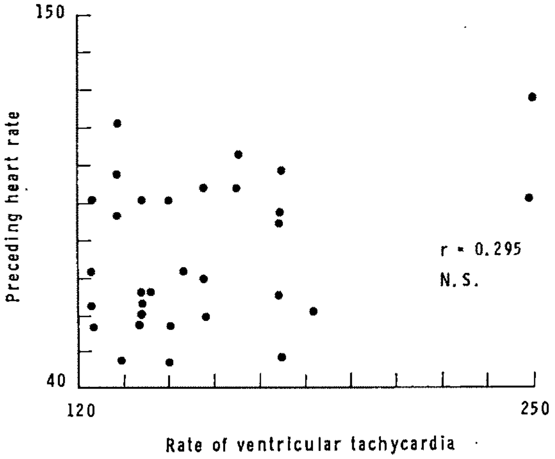

Fig. 3 *Relation of the preceding heart rate to the rate of ventricular tachycardia.*

(B) PREMATURITY INDEX

(i) *Prematurity index and rate of ventricular arrhythmia*

A significant inverse correlation between the prematurity index and the rate of the following accelerated idioventricular rate or ventricular tachycardia was observed ($r=-0{\cdot}506$; $p<0{\cdot}001$) (Fig. 6). In addition, the prematurity index preceding accelerated idioventricular rate was significantly longer than the prematurity index preceding ventricular tachycardia (1·89 ±0·53 and 1·32 ±0·48, respectively) ($2p<0{\cdot}001$) (Fig. 4).

(ii) *Prematurity index in patients with and without ventricular tachycardia*

There was no significant difference when the prematurity index of both isolated ventricular extrasystoles and repetitive ventricular arrhythmia were compared in patients with and without ventricular tachycardia (1·31 ±0·38 in patients with ventricular tachycardia and 1·45 ±0·52 in those without it).

(C) ISOLATED VENTRICULAR EXTRASYSTOLES

Forty-three of the 44 patients studied had ventricular arrhythmias during the 24-hour period.

(i) *Incidence of ventricular extrasystoles related to time after chest pain*

The number of isolated ventricular extrasystoles decreased significantly from 75·68 ±122·6 in the

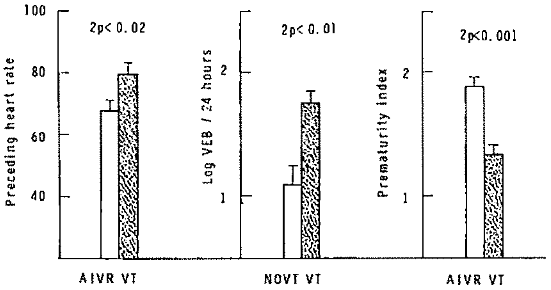

Fig. 4 *Comparison of prematurity index, preceding heart rate, and the frequency of isolated ventricular extrasystole (VEB) in patients with accelerated idioventricular rhythm and ventricular tachycardia (AIVR and VT).*

first 24 hours to $40{\cdot}98 \pm 87{\cdot}25$ in the second 24 hours (paired "t" test $2p < 0{\cdot}05$).

(ii) *Relation to incidence of accelerated idioventricular rate and ventricular tachycardia*

Because the frequency of isolated ventricular extrasystole is not normally distributed, the data were expressed as logarithms before applying Student's "t" test.[8] In patients showing ventricular tachycardia, the $\log_{10}$ ventricular extrasystole was $1{\cdot}75 \pm 0{\cdot}45$ as compared with $1{\cdot}11 \pm 0{\cdot}87$ in patients without ventricular tachycardia ($2p < 0{\cdot}01$) (Fig. 4). In addition patients showing ventricular tachycardia and accelerated idioventricular rate had a significantly greater frequency of isolated ventricular extrasystoles as compared with patients showing neither rhythm ($1{\cdot}71 \pm 0{\cdot}70$ in patients with tachycardia and/or accelerated rhythm and $0{\cdot}83 \pm 0{\cdot}66$ in patients without either) ($2p < 0{\cdot}001$). This suggests that patients with repetitive ventricular rhythms have more frequent isolated ventricular extrasystoles. This is even more pronounced in patients with ventricular tachycardia.

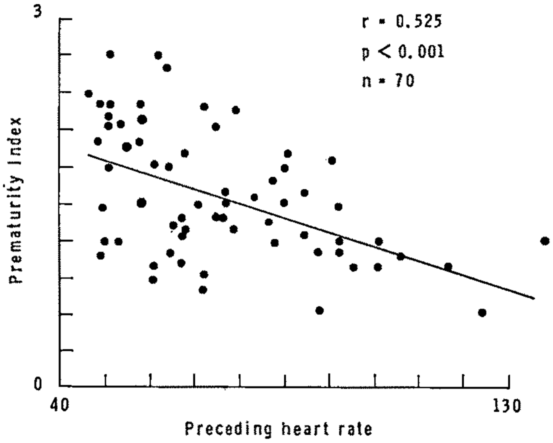

Fig. 5 *Relation of preceding heart rate to the prematurity index.*

(D) COUPLETS AND TRIPLETS

The incidence of couplets and triplets was 55 per cent and 34 per cent, respectively. Though both tended to be higher in patients with ventricular tachycardia (75% and 50%, respectively) as compared with patients without ventricular tachycardia (43% and 25%), this was not statistically significant.

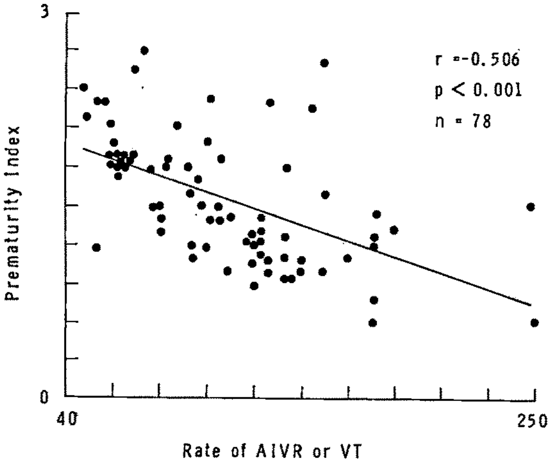

Fig. 6 *Relation of prematurity index to the rate of ventricular arrhythmia (AIVR or VT).*

(E) ASSOCIATION OF VENTRICULAR TACHYCARDIA AND ACCELERATED IDIOVENTRICULAR RHYTHM

We did not see any particular tendency for accelerated idioventricular rhythm and ventricular tachycardia to coexist in eight patients having both, eight with ventricular tachycardia only, and nine with accelerated idioventricular rhythm only.

(F) ANALYSIS OF DATA WITH RELATION TO TIME

The relation of preceding heart rate to the prematurity index and to the rate of accelerated idioventricular rhythm or ventricular tachycardia was similar in the first and second 12 hours of recording, and in patients presenting within or after six hours of pain. Similarly, the relation between the prematurity index and the rate of accelerated idioventricular rhythm or ventricular tachycardia was independent of time.

(G) INFLUENCE OF DRUGS ON RELATION BETWEEN PRECEDING HEART RATE, PREMATURITY INDEX, AND RATE OF ACCELERATED IDIOVENTRICULAR RHYTHM AND VENTRICULAR TACHYCARDIA

Fourteen patients were on beta-blocking drugs during the period of tape-recording. The correlations between (1) preceding heart rate and prematurity index; (2) preceding heart rate and the rate of accelerated idioventricular rhythm and ventricular tachycardia; and (3) prematurity index and the rate of accelerated idioventricular rhythm and ventricular tachycardia were calculated in patients with and without beta-blocker treatment (Table). Similar correlations were found in all instances except one in the beta-blocker group, where no significant relation between preceding heart rate and the rate of accelerated idioventricular rhythm and ventricular tachycardia was observed. This suggests that the change in the prematurity index occurring at different heart rates is independent of any direct pharmacological action of beta-blockers and is probably related to heart rate changes *per se.*

Lignocaine was used in six patients within an hour of admission: four after ventricular fibrillation; and two for frequent ventricular tachycardia. In two other patients lignocaine was given after frequent runs of ventricular tachycardia were observed by the coronary care unit nurses approximately two hours after admission. This was continued for 24 hours as a continuous infusion and produced almost complete suppression of any ventricular tachycardia or accelerated idioventricular rhythm in these patients. It was therefore not possible to assess if the relation between preceding heart rate, prematurity index, and rate of sustained ventricular arrhythmia was altered by lignocaine.

Table *Correlations between preceding heart rate, prematurity index, and rate of ventricular arrhythmia in patients treated and not treated with beta-blocker*

	Patients on beta-blocker	*Patients not on beta-blocker*
Preceding heart rate and rate of ventricular arrhythmia	n=18 r=0·260 NS	n=68 r=0·473 p<0·001
Preceding heart rate v prematurity index	r= −0·483 p<0·05	r= −0·673 p<0·001
Prematurity index v rate of ventricular rhythm	r= −0·687 p<0·01	r= −0·574 p<0·001

(H) CHARACTERISTICS OF PATIENTS WITH VENTRICULAR FIBRILLATION

Four patients developed ventricular fibrillation within an hour of admission and all four showed separate runs of ventricular tachycardia two to 30 minutes before the episode of ventricular fibrillation compared with only one of four patients showing accelerated idioventricular rhythm. Three patients had preceding ventricular tachycardia with rates 170, 178, and 178/min. In one of these, an episode of ventricular tachycardia at 178/min deteriorated into ventricular fibrillation. The fourth patient had ventricular tachycardia at a rate of 138/min. In comparison only two out of the 40 patients without ventricular fibrillation had ventricular tachycardia at rates exceeding 170/min. In the first three patients the fibrillation was initiated by R on T ventricular extrasystoles (prematurity index = 0·62, 0·62, and 0·80, respectively). The fourth episode of ventricular fibrillation was initiated by an extrasystole falling at the end of the descending limb of the T wave (prematurity index = 0·90). In comparison, no patient without fibrillation showed a prematurity index less than 0·80. Two patients without fibrillation showed R on T extrasystoles (prematurity index = 0·82 and 0·84) one of whom also showed a run of ventricular tachycardia (170/min). Therefore patients with ventricular fibrillation showed faster ventricular tachycardia rates and earlier extrasystoles before the episode.

Discussion

Lown *et al.*[4] defined a series of types of ventricular arrhythmia which were thought to be associated with an increased risk of ventricular fibrillation. Other workers have supported this original concept.[9–11] Recent reports, however, do not support this and ventricular fibrillation has been reported to occur without warning arrhythmias.[12 13] In addition warning arrhythmias have been found to be equally common in patients with and without ventricular fibrillation.[5 7 14] Since the incidence of ventricular fibrillation is relatively low in patients in hospital because of the delay in admission (20 out of 850 admissions in one series),[15] many investigators[5 6 10] have looked at the precursors of ventricular tachycardia which are known to be associated with a high mortality. In our own study all four patients with ventricular fibrillation demonstrated ventricular tachycardia, with three having ventricular rates of 170/min or more before the episode. We have therefore studied "warning arrhythmias" before ventricular tachycardia occurs.

Like previous authors,[5 10] we have observed a higher incidence of isolated ventricular extrasystoles in patients with ventricular tachycardia. Though couplets and triplets were more frequent in patients with ventricular tachycardia as compared with those without ventricular tachycardia, this difference did not reach statistical significance. We have also shown a significant decrease in the incidence of ventricular extrasystoles with increasing time from onset of chest pain, as the delay in the onset of tape-recording would affect the probability of detecting warning arrhythmia.[16] Further, Lie *et al.*[7] have suggested that time after onset of chest pain should be an important criterion for the institution of anti-arrhythmic therapy.

In this study we have chosen a new and quantitative approach to study the relation between preceding heart rate, prematurity index, and the rate of accelerated idioventricular rhythm and ventricular tachycardia. To use sharp distinctions of R on T and non-R on T is not wholly accurate as there can be ventricular extrasystoles with widely differing prematurity indices in each category. Similarly the rate of ventricular tachycardia or accelerated idioventricular rhythm is more accurate than arbitrary definitions (about which there is no unanimity)[17] as the rates may vary within each category. We have, therefore, chosen to measure the individual prematurity index and relate it to the rate of the accompanying ventricular arrhythmia.

We have demonstrated a significant inverse correlation between the prematurity index and the rate of ventricular arrhythmia. However, Fig. 6 shows considerable scatter and it is evident that in some individual instances short prematurity index did not always lead to ventricular tachycardia. We have also shown that ventricular tachycardia is preceded by extrasystoles with a prematurity index significantly shorter than those preceding accelerated idioventricular rhythm. However, when we compared the prematurity index in patients with and without ventricular tachycardia, no significant difference was obtained, consistent with the observations of De Soyza *et al.*[5] and Chou and Wenzke.[6] The possible reasons for this apparent discrepancy should be considered. The early studies of Smirk[1] and Bleifer *et al.*,[2] though stressing that the R on T ventricular extrasystole was associated with a higher incidence of ventricular fibrillation and tachycardia, also showed that this did not always happen. It was Bleifer *et al.*[2] who demonstrated that R on T extrasystoles alone did not carry a serious prognosis but that when seen in combination with repetitive ventricular arrhythmia they were dangerous. In fact, the majority of Smirk's patients showed both the R on T phenomenon and couplets, though this was not discussed in his paper. Further, Dolara[18] has shown that the QT interval may be prolonged and when associated with a slightly premature extrasystole this gives the appearance of an R on T; this may have a different significance. Recently Greene *et al.*[19] have reported that artificial cardiac stimulation leading to repetitive ventricular activity in patients after myocardial infarction could identify patients prone to ventricular tachycardia and sudden death. It is possible that only in such patients whose ventricles are "vulnerable" to ventricular tachycardia is the R on T extrasystole of importance. In other patients it may not have the same significance.

Reports that late ventricular ectopic beats may initiate ventricular fibrillation and tachycardia do not necessarily contradict the role of the R on T extrasystole in their causation. Firstly, several factors (for example critical mass of myocardium available for re-entry, critical relation between conduction velocity and refractory period in certain parts of the myocardium, local myocardial electrolyte changes, disturbances of nervous regulation, etc.) other than an extrasystole falling in the "vulnerable period" may affect the response of the ventricle regarding the development of ventricular tachycardia and fibrillation.[20] Secondly, Waldo and Kaiser[21] have shown, using epicardial recordings, that localised fibrillation occurring in the infarct zone continues after the T wave of the surface electrocardiogram and that this was often associated with the development of ventricular tachycardia and fibrillation. It may therefore be possible that ventricular extrasystoles occurring apparently after the T wave on surface recordings may be occurring during the period of fragmented electrical activity when the ventricle may be "vulnerable".

We have shown a significant relation between preceding heart rate and the rate of sustained ventricular arrhythmia. This relation appears to be mainly for accelerated idioventricular rhythm and not for ventricular tachycardia. This observation supports the possibility that accelerated idioventricular rhythm is usually an escape rhythm.[17] However, the heart rate preceding runs of ventricular tachycardia was significantly higher than that preceding accelerated idioventricular rhythm. Lie *et al.*[7] have reported a higher incidence of sinus tachycardia immediately preceding ventricular fibrillation. Recent experimental work[22] has shown that a rapid heart rate may increase ventricular extrasystoles, non-homogeneity of refractory periods in contiguous areas of the myocardium, and vulnerability to ventricular fibrillation. In addition slow heart rates caused by vagal stimulation *per se* also increased ventricular fibrillation threshold. These considerations support our observations of a direct relation between heart rate and the rate of ventricular arrhythmia.

A significant inverse correlation between preceding heart rate and the prematurity of the ventricular ectopic has been shown. This may indicate that increasing heart rates may lead to ventricular ectopic beats with shorter prematurity index. The possibility that this may be an artefact must be considered. It is possible that as heart rate increases, and the RR interval decreases, the coupling interval of a manifest ventricular extrasystole may shorten correspondingly. However the QT interval also shortens with increasing heart rate and therefore any shortening of the prematurity index at fast heart rates is likely to be real and not artefact. However, the underlying mechanism for this relation is unclear and we are not aware of any work relating heart rates to the prematurity index.

We have shown that faster heart rates are associated with ventricular ectopic beats with shorter prematurity, which may in turn lead to faster ventricular arrhythmia in "susceptible" patients. This relation, however, may not exist in patients not susceptible to repetitive ventricular arrhythmias.

References

1 Smirk FH. R waves interrupting T waves. *Br Heart J* 1949; **11**: 23–36.

2 Bleifer SB, Karpman HL, Sheppard JJ, Bleifer DJ. Relation between premature ventricular complexes and development of ventricular tachycardia. *Am J Cardiol* 1973; **31**: 400–3.

3 Wiggers CJ, Wegria R, Pinera B. The effects of myocardial ischemia on fibrillation threshold: the mechanism of spontaneous ventricular fibrillation following coronary occlusion. *Am J Physiol* 1940; **131**: 309–16.

4 Lown B, Fakhro AM, Hood WB Jr, Thor GW. The coronary care unit. New perspectives and directions. *JAMA* 1967; **199**: 188–98.

5 De Soyza N, Bissett JK, Kane JJ, Murphy ML, Doherty JE. Ectopic ventricular prematurity and its relationship to ventricular tachycardia in acute myocardial infarction in man. *Circulation* 1974; **50**: 529–33.

6 Chou TC, Wenzke F. The importance of R on T phenomenon. *Am Heart J* 1978; **96**: 191–4.

7 Lie KI, Wellens HJJ, Downar E, Durrer D. Observations on patients with primary ventricular fibrillation complicating acute myocardial infarction. *Circulation* 1975; **52**: 755–9.

8 Ahumada GG, Karlsberg RP, Jaffe AS, Ambos HD, Sobel BE, Roberts R. Reduction of early ventricular arrhythmia by acebutolol in patients with acute myocardial infarction. *Br Heart J* 1979; **41**: 654–9.

9 Lawrie DM, Higgins MR, Godman MJ, Oliver MF, Julian DG, Donald KW. Ventricular fibrillation complicating acute myocardial infarction. *Lancet* 1968; **ii**: 523–8.

10 Mogensen L. Ventricular tachyarrhythmias and lignocaine prophylaxis in acute myocardial infarction. *Acta Med Scand* 1970; suppl: 513.

11 Julian DG, Valentine PA, Miller GG. Disturbances of rate, rhythm and conduction in acute myocardial infarction. A prospective study of 100 consecutive unselected patients with the aid of electrocardiographic monitoring. *Am J Med* 1964; **37**: 915–27.

12 Bennett MA, Pentecost BL. Warning of cardiac arrest due to ventricular fibrillation and tachycardia. *Lancet* 1972; **i**: 1351–2.

13 Skjaeggestad O, Berstad A. Arrhythmias in the earliest phase of acute myocardial infarction. *Acta Med Scand* 1974; **196**: 271–4.

14 El-Sherif N, Myerburg RJ, Scherlag BJ, *et al.* Electrocardiographic antecedents of primary ventricular fibrillation. Value of the R-on-T phenomenon in myocardial infarction. *Br Heart J* 1976; **38**: 415–22.

15 Dhurandhar RW, MacMillan RL, Brown KWG. Primary ventricular fibrillation complicating acute myocardial infarction. *Am J Cardiol* 1971; **27**: 347–51.

16 Campbell RWF, Murray A. Significance of arrhythmias in the early and late phase of myocardial infarction. In Hjalmarson Å, Wilhelmsen L, eds. *Acute and long-term medical management of myocardial ischaemia.* Mölndal, Sweden: Hässle, 1978: 130–6.

17 Bigger JT Jr, Dresdale RJ, Heissenbuttel RH, Weld FM, Wit AL. Ventricular arrhythmias in ischemic heart disease: mechanism, prevalence, significance, and management. *Prog Cardiovasc Dis* 1977; **19**: 255–300.

18 Dolara A. Early premature ventricular beats, repetitive ventricular response, and ventricular fibrillation. *Am Heart J* 1967; **74**: 332–6.

19 Greene HL, Reid PR, Schaeffer AH. The repetitive ventricular response in man: a predictor of sudden death. *N Engl J Med* 1978; **299**: 730–4.

20 Surawicz B. Ventricular fibrillation. *Am J Cardiol* 1971; **28**: 268–87.

21 Waldo AL, Kaiser GA. A study of ventricular arrhythmias associated with acute myocardial infarction in the canine heart. *Circulation* 1973; **47**: 1222–8.

22 Kent KM, Smith ER, Redwood DR, Epstein SE. Electrical stability of acutely ischemic myocardium: influences of heart rate and vagal stimulation. *Circulation* 1973; **47**: 291.

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Response of atrial flutter to overdrive atrial pacing and intravenous disopyramide phosphate, singly and in combination

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SUMMARY Ten patients who suffered spontaneous paroxysms of atrial flutter were investigated by electrophysiological techniques. Two had overt Wolff-Parkinson-White syndrome; three Lown-Ganong-Levine syndrome; and one a concealed accessory atrioventricular connection. Atrial flutter was initiated, at study, by right atrial pacing and electrograms from the right atrium and coronary sinus were observed for at least five minutes to ensure stable flutter in both atria.

Atrial flutter was terminated by 2·5 s or 5 s bursts of atrial pacing at rates 10, 50, or 100 beats/min faster than the intrinsic flutter rate in only two patients. Atrial flutter, which was reinitiated in two patients, was then treated with intravenous disopyramide phosphate, 2 mg/kg body weight, infused over five minutes. In all 10 patients the atrial rate slowed from a mean of 310±39 beats/min to 217±27 beats/min and atrial flutter terminated in one case. Though the mean ventricular rate fell from 161±52 beats/min to 156±45 beats/min the atrioventricular conduction ratio fell from 2·17±0·86 to 1·55±0·59 and four patients were left with symptomatically significant increases of ventricular rate. In seven of nine patients overdrive atrial pacing, repeated after disopyramide, resulted in the conversion of atrial flutter to sinus rhythm.

In this study, overdrive atrial pacing and intravenous disopyramide, singly and in combination, terminated atrial flutter in nine of the 10 patients and it is suggested that this method may provide an effective alternative to direct current cardioversion.

In 1967, Haft and coworkers[1] reported the successful termination of atrial flutter by rapid atrial pacing. They also suggested that premedication with quinidine-like drugs potentiated the success of the technique. Though others[2–11] have used atrial pacing techniques to treat atrial flutter with variable and, at times, contradictory results[12 13] little attention has been given to pretreatment with antiarrhythmic agents. Here we report the individual and combined results of overdrive atrial pacing and intravenous disopyramide phosphate in the treatment of paroxysms of atrial flutter.

Subjects and methods

Ten patients aged between 22 and 62 years were investigated for complaints of recurrent paroxysmal palpitations (Table 1). All patients had suffered documented attacks of atrial flutter and three patients also had attacks of "supraventricular" tachycardia which were not thought to be atrial flutter. One patient presented with profound sinus bradycardia, sinus node arrest, and paroxysms of tachycardia. There was no clinical or radiographic evidence of organic heart disease though two patients were mildly hypertensive. The surface electrocardiogram was normal in four patients, showed sinus bradycardia in one, and a short PR interval in five. In two patients, the short PR interval was followed by broad QRS complexes of the Wolff-Parkinson-White pattern, type A. Routine blood tests, including thyroid function tests, were normal in all patients.

The patients underwent intracardiac electrophysiological investigation in the catheterisation laboratory or coronary care unit. All patients were studied in a fasting unsedated state and had not received medication for at least 72 hours before the study. Informed consent was obtained from each patient. Conventional electrophysiological investigations were performed as described elsewhere,[14]

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but for the purpose of this study bipolar electrodes were positioned to record simultaneously or sequentially from the lateral wall of the right atrium (close to its junction with the superior vena cava) and the coronary sinus. Atrial flutter was initiated by rapid atrial pacing and the arrhythmia was observed for five minutes to ensure that there was stable flutter of both atria. At the end of this period, attempts were made to terminate atrial flutter by atrial pacing from the single right atrial site at a stimulus voltage of twice the diastolic threshold during sinus rhythm. Pacing rates were adjusted to 10, 50, and 100 beats/min faster than the spontaneous flutter rate and pacing was continued for periods of two and a half and five seconds. If this resulted in the successful termination of the arrhythmias, atrial flutter was restimulated and reobserved for a further five minutes to ensure stability. Disopyramide phosphate, at a dose of 2 mg/kg body weight, was then administered to all 10 patients. The infusion was given evenly over exactly five minutes, and continuous electrocardiographic recordings at a paper speed of 25 mm/s were made for a period of 10 minutes. Short strips were recorded at 100 mm/s at one minute intervals.

If atrial flutter had not terminated in response to disopyramide within 10 minutes of the start of the infusion, rapid atrial pacing for durations of two and a half and five seconds, at rates 10, 50, and 100 beats/min faster than the new flutter frequency, was again tried.

Atrial and ventricular rates were measured at one minute intervals throughout the study. Where the ventricular rate was irregular, the mean rate over a 10 second period was calculated. The atrioventricular conduction ratios were derived from these values. The maximum ventricular rate during the study period was noted. Results were analysed by the paired Student's t test.

Table 1 *Clinical, electrocardiographic, and electrophysiological details of 10 patients with recurrent paroxysmal atrial flutter*

Case no.	*Age (y)· sex*		*Diagnosis*	*EPS*
1	31	M	PAFl, SVT, LGL	PAFl, AVRT(CLAP)
2	44	M	PAFl	PAFl
3	39	F	PAFl, SAD, LGL	PAFl, SAD
4	62	M	PAFl, LGL	PAFl
5	22	F	PAFl	PAFl
6	58	M	PAFl	PAFl
7	48	M	PAFl	PAFl
8	62	M	PAFl, SVT, WPW	PAFl, AVRT(LAP)
9	48	M	PAFl, SVT, WPW	PAFl, AVRT(LAP)
10	52	M	PAFl	PAFl

PAFl, paroxysmal atrial flutter; SVT, supraventricular tachycardia; LGL, Lown-Ganong-Levine syndrome; SAD, sinuatrial disease; WPW, Wolff-Parkinson-White syndrome; AVRT, atrioventricular re-entrant tachycardia; CLAP, concealed left-sided accessory pathway; LAP, left-sided accessory pathway; EPS, electrophysioogical study diagnosis.

Results

The results of routine electrophysiological studies in the 10 patients are summarised in Table 1. In six patients, no electrophysiological abnormality could be detected, but in one, abnormal sinus node function was documented and, in three, left-sided accessory atrioventricular pathways were disclosed and re-entrant tachycardias, using these pathways in the retrograde direction, were precipitated.

In all 10 patients, stable atrial flutter of both chambers was initiated by atrial pacing. The initial flutter frequency, the ventricular response rate, and the atrioventricular ratio are set out in Table 2, and illustrated in Fig. 1 and 2. The flutter rate varied between 230 beats/min and 375 beats/min (mean = 310±39 beats/min), and in eight cases characteristic "saw tooth" flutter waves were seen, but, in two, both with overt Wolff-Parkinson-White syndrome, baseline oscillations were obscured

Table 2 *Response of atrial flutter to disopyramide (diso) and overdrive atrial pacing (RAP)*

Case no.	*Atrial rate*		*Ventricular rate*			*A/V ratio*		*Termination*		
	Pre	*Post*	*Pre*	*Max*	*Post*	*Pre*	*Post*	*Diso*	*RAP(pre)*	*RAP(post)*
1	320	220	130	171	130	2·46	1·69	0	0	+
2	353	230	86	110	90	4·10	2·55	+	0	NR
3	300	176	150	220	176	2·00	1·00	0	0	+
4	336	264	156	156	138	2·15	1·91	0	+	0
5	328	256	164	164	128	2·00	2·00	0	+	+
6	375	207	125	130	88	3·00	2·35	0	0	0
7	280	210	140	210	210	2·00	1·00	0	0	+
8	230	188	230	230	188	1·00	1·00	0	0	+
9	280	194	280	280	194	1·00	1·00	0	0	+
10	300	220	150	220	220	2·00	1·00	0	0	+
Mean	310	217	161	189	156	2·17	1·55			
SD (±)	39	27	52	49	45	0·86	0·59			

pre, pre-disopyramide; post, post-disopyramide; max, maximum ventricular rate observed during 10-minute observation period after the start of the disopyramide infusion; +, successful conversion; 0, unsuccessful conversion; NR, not relevant.

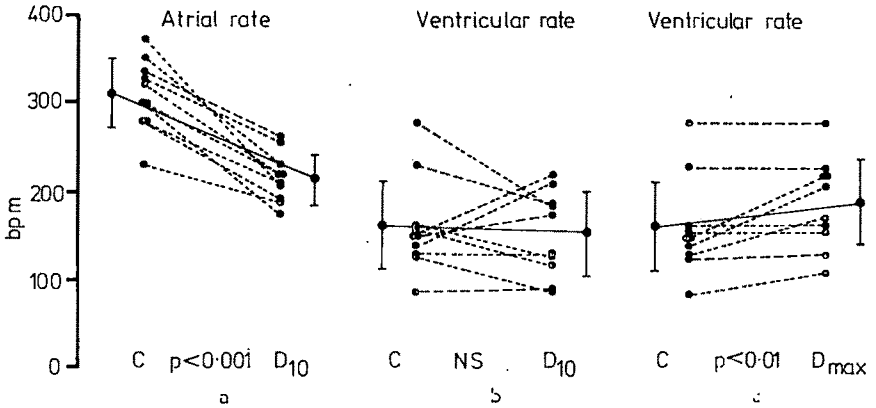

Fig. 1 *Atrial and ventricular rates before and after disopyramide infusion. C, control;* D_{10}*, 10 minutes after disopyramide;* D_{max}*, maximum ventricular rate during the 10 minute observation period after the start of the disopyramide infusion; bpm, beats per minute.*

by 1:1 conduction over the accessory pathway.

Rapid atrial pacing, before disopyramide (Fig. 3) successfully terminated two examples of atrial flutter (cases 4 and 5). In the remainder, flutter was entrained (six cases) or atrial capture was not achieved (two cases).

The infusion of disopyramide phosphate resulted in reduction of the atrial rate in all patients. The mean atrial rate fell significantly ($p < 0{\cdot}001$) from 310±39 beats/min to 217±27 beats/min (Fig. 1a). In one patient atrial flutter terminated six minutes after the start of the disopyramide infusion. The ventricular rate response to disopyramide infusion was variable. Fig. 4 illustrates the response in case 9. Initially, the atrioventricular rate was 280 beats/min, and five minutes after the conclusion of the disopyramide infusion the 1:1 atrioventricular relation persisted at a rate of 194 beats/min. In case 7 (Fig. 5) 2:1 atrioventricular conduction was present initially but, in response to disopyramide, the atrial rate slowed from 270 beats/min to 200 beats/min with the development of 1:1 atrioventricular conduction. Results in the 10 patients are illustrated in Fig. 6 and are demonstrated graphically in Fig. 1b and 1c. In six patients, the ventricular rate increased at some time during the 10 minute observation period (Fig. 1c) and the mean increase (161±52 to 189±49 beats/min) was significant ($p < 0{\cdot}01$). By the end of the observation period (Fig. 1b) there was an insignificant fall in the mean ventricular rate (161±57 to 156±45 beats/min), but the atrioventricular conduction ratio had significantly ($p < 0{\cdot}01$) fallen (2·17±0·86 to 1·55±0·59).

In nine patients, the termination of the arrhythmia by overdrive atrial pacing was attempted again after the infusion of disopyramide. The technique proved successful in seven cases, six of whom had not responded before disopyramide. In the two failures it was not possible to achieve atrial capture. In the successful cases, atrial pacing usually resulted in transient runs of atrial tachycardia or fibrillation before conversion to sinus rhythm. Atrial fibrillation of a duration longer than 5 s was not precipitated except in the two failures, who after completing the study were subjected to longer and faster periods of atrial pacing. One of these patients eventually required direct current cardioversion. The overall results of the combined technique are illustrated in Fig. 7.

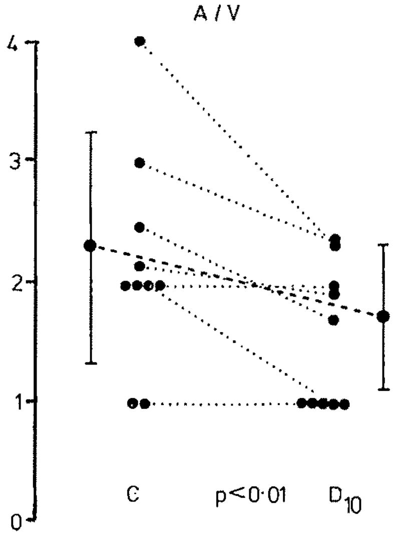

Fig. 2 *The atrioventricular (A/V) ratio before (C) and after* (D_{10}) *disopyramide infusion.*

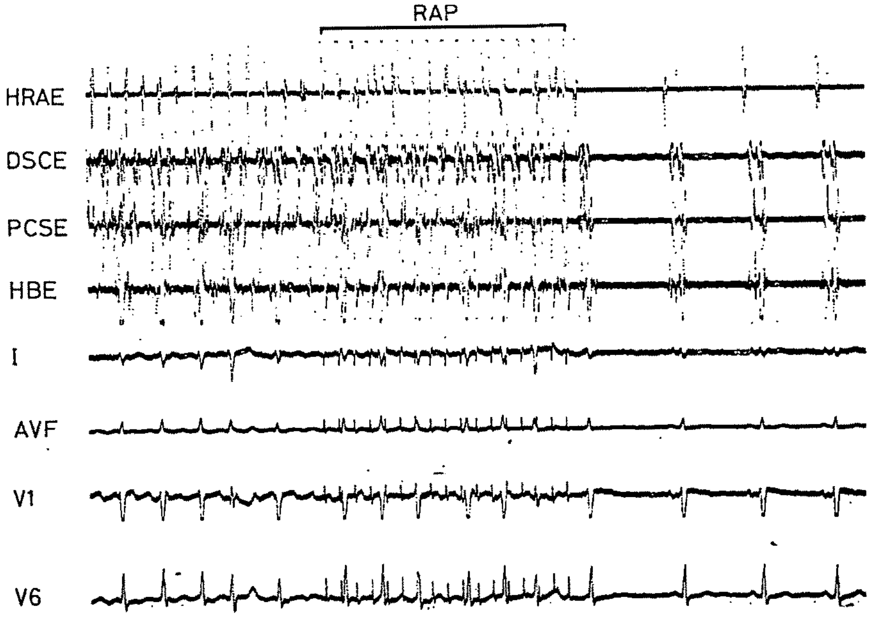

Fig. 3 *The successful conversion of atrial flutter by rapid atrial pacing before the administration of disopyramide (case 4). The atrial flutter rate is 336 beats/min; the average ventricular rate is 156 beats/min; and the atrial pacing rate is 386 beats/min for 2·5 seconds.*
HRAE, high right atrial electrogram; DCSE, distal coronary sinus electrogram; PCSE, proximal coronary sinus electrogram; HBE, His bundle region electrogram; RAP, rapid atrial pacing; 1, aVF, V1, and V6 are surface electrocardiogram leads; paper speed, 25 mm/s.

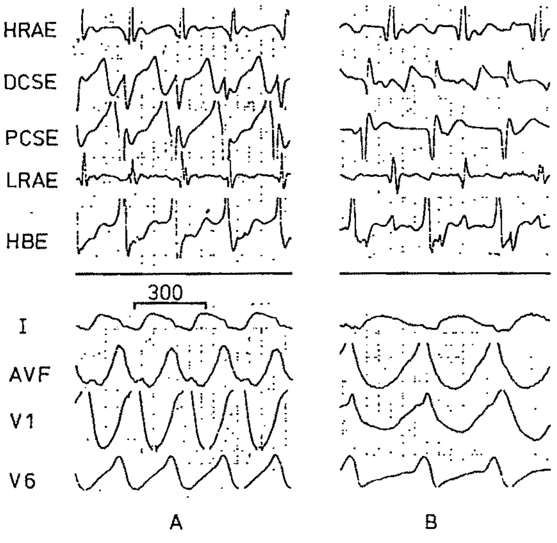

Fig. 4 *Atrial flutter with 1:1 AV conduction via a left-sided accessory atrioventricular pathway before and 10 minutes after the infusion of disopyramide. The rate falls from 280 beats/min to 194 beats/min (case 9). LRAE, low right atrial electrogram. Paper speed, 100 mm/s.*

Discussion

In 1963, Moe *et al.*[15] showed that paced atrial extrastimulation could interrupt experimental reciprocating atrioventricular nodal tachycardia, and recently Wit and Cranefield[16] showed that triggered tachycardias would also stop in response to premature stimulation. Massumi *et al.*[17] first applied artificial pacing methods to the treatment of supraventricular tachycardia, and Durrer and colleagues[18] confirmed these clinical results and stressed that the termination of tachycardia by premature beats required critical timing. When a single premature beat will suffice it may be simply provided by fixed rate underdrive pacing,[11] but if several depolarisations are required, overdrive pacing may be necessary. The termination of supraventricular tachycardia by overdrive atrial pacing was first reported in 1968[19]; by 1972, it was an accepted alternative to direct current cardioversion,[20] and it is now recognised as a very successful method for the termination of the majority of supraventricular tachycardias.[21]

Since the report by Haft *et al.* in 1967,[1] other investigators have confirmed that atrial flutter may be successfully converted to sinus rhythm by overdrive atrial pacing, but there have been several dissenting reports. Puech *et al.*[12] succeeded in terminating immediately only six of 29 cases of atrial flutter and in 22 atrial fibrillation was the result. In six of these, however, the atrial fibrillation lasted only a few seconds. Rosen and colleagues[13] treated 15 cases by overdrive atrial pacing: none reverted to sinus rhythm, but "stable" atrial fibrillation was induced in six patients. Our results were similarly poor before the administration of disopyramide. The poor results are probably a result of limiting the duration of pacing, the pacing rate, and the pacing energy. These limitations, which have not specifically been applied by others, were designed to minimise the risk of precipitating atrial fibrillation which did not occur in this series.

Disopyramide phosphate, a butyramide derivative, has been shown to reduce the frequency of automatically discharging foci and to slow the conduction velocity in both myocardial and specialised conduction tissue.[22, 23] In addition to its membrane stabilising effect disopyramide increases the duration of the action potential[23] and, in man, may prolong the atrial refractory period.[24, 25] Though the mechanism of atrial flutter is controversial,[26] some suggesting that abnormal automaticity[27, 28] is the cause and others preferring a re-entrant basis,[29–31] whichever the mechanism the electrophysiological properties of disopyramide could explain both the termination and the slowing of atrial flutter. If circus movement sustains the arrhythmia decreased atrial conduction velocity would lead to slowing of the flutter rate but, if atrial refractoriness increased sufficiently to exceed the tachycardia cycle length, the arrhythmia would be extinguished. Alternatively, the depressant effect of disopyramide on spontaneous diastolic depolarisation would result in slowing, and possibly termination of atrial flutter caused by enhanced atrial automaticity. Decreased atrial excitability[32] induced by disopyramide may also contribute to the termination of atrial flutter.

The effect of disopyramide on atrial flutter has not been reported in detail. Though Luoma *et al.*[33] studied patients with atrial flutter, they did not distinguish this arrhythmia from atrial fibrillation. In the cases reported by Vandenbosch *et al.*,[34] disopyramide converted three of 11 examples of atrial flutter and, in the series of Deano *et al.*,[35] three of eight patients reverted to sinus rhythm in response to disopyramide. Our rate of success with conversion was comparatively low and while this may be partly related to the short observation period, previous experience with intravenous disopyramide indicated that the majority of terminations occurred within 10 minutes of the start of the infusion[36] and, in any event, it is difficult to ascribe late terminations to the action of the drug.[37]

In this series, as in others,[34, 35] disopyramide resulted in consistent and pronounced slowing of the atrial flutter frequency. In the presence of 1:1 atrioventricular conduction, the ventricular rate also slowed, but when a degree of atrioventricular conduction block was present, the infusion

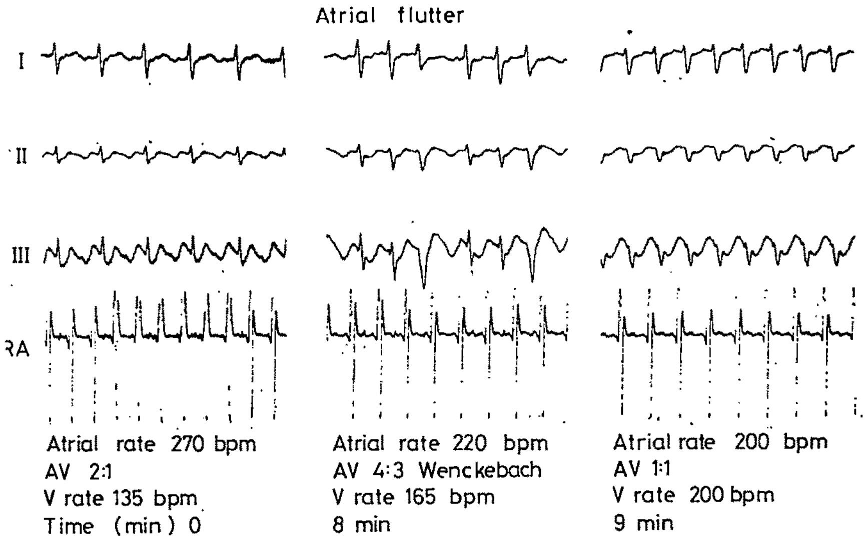

Fig. 5 *Atrial flutter before (0) and 8 and 9 minutes after the infusion of disopyramide (case 7). See text for discussion. I, II, III are surface electrocardiogram leads. RA, right atrial electrogram. Paper speed, 25 mm/s.*

of disopyramide resulted in higher ventricular rates in six cases. This result is a potential hazard when treating atrial flutter with disopyramide, and represents the combined effects of slowing of flutter frequency and anticholinergic effects on the atrioventricular node.[25] [38] [39] When 1:1 atrioventricular conduction occurs after the treatment of atrial flutter with disopyramide the flutter frequency is considerably less than the pretreatment rate and *very* rapid ventricular rates do not result. Nevertheless, if disopyramide does not achieve conversion of atrial flutter to sinus rhythm the combination of increased ventricular rates and depressed myocardial function could lead to significant symptomatic deterioration and systemic hypotension. This serious side effect was not encountered in this study. Similar effects have been observed with quinidine[40–42] and procainamide.[43]

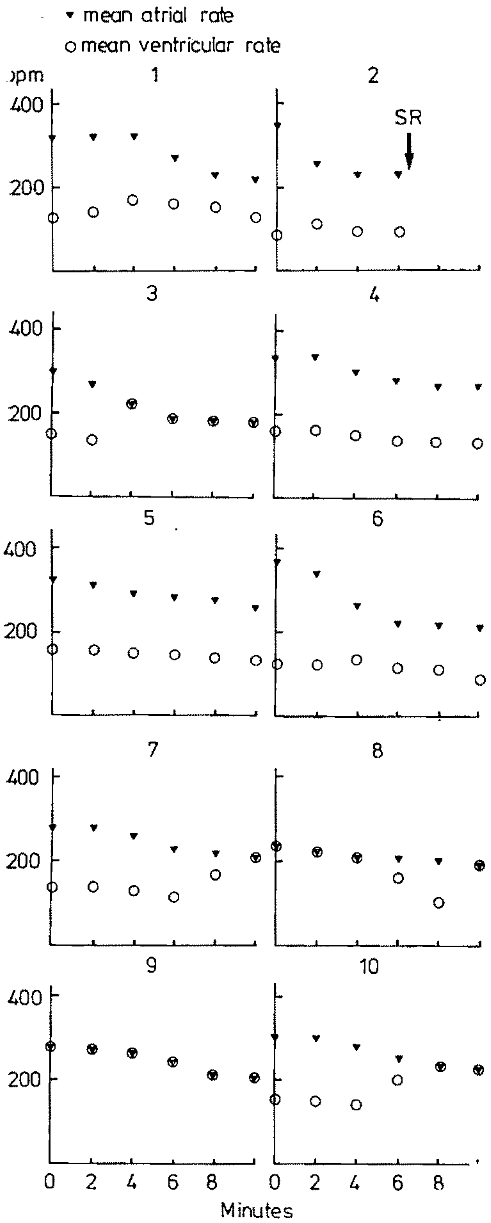

Fig. 6 *Atrial and ventricular responses at 0, 2, 4, 6, 8, and 10 minutes, after disopyramide infusion in cases 1 to 10.*

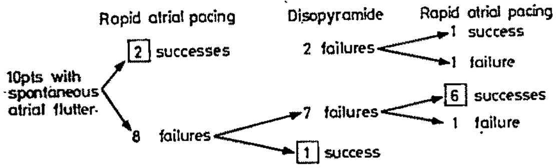

Fig. 7 *Successful and unsuccessful conversion to sinus rhythm in 10 cases of atrial flutter.*

The possibility that premedication with a quinidine-like antiarrhythmic agent would potentiate the conversion of atrial flutter to sinus rhythm by overdrive atrial pacing was suggested by Haft *et al.*[1] In one of their cases, rapid atrial pacing was effective only after administration of oral procainamide. In a recent report by Wyndham *et al.*[44] pretreatment with disopyramide reduced the risk of atrial pacing precipitating atrial fibrillation and improved the chances of successful conversion of atrial flutter to sinus rhythm.

This study has attempted to assess systematically the value of premedication of atrial flutter with disopyramide before overdrive atrial pacing, and the results suggest that the conversion rate to sinus rhythm is improved. If atrial flutter were a result of circus movement, an increase of atrial refractoriness after disopyramide might increase the physiological obstacle around which the flutter wavelet circulated[45] allowing pacing closer to an enlarged circuit. Alternatively, if conduction slowed without a commensurate increase of refractoriness the excitable gap between the tachycardia depolarisation wavefront and its receding repolarised tail would increase. Either result would facilitate the invasion and "saturation" of the tachycardia circuit by pacemaker-induced depolarisation. On the other hand, if flutter were the result of abnormal automaticity, a disopyramide-induced reduction in the discharge rate would improve the electrophysiological access to the focus of the arrhythmia, unless disopyramide produced conspicuous increases in atrial refractoriness or conduction times.

Paroxysmal atrial flutter is difficult to treat effectively. Medical conversion of an individual paroxysm with drugs such as verapamil,[46] beta-blockers,[47] quinidine,[41] and disopyramide,[34–36] is generally disappointing and though synchronised direct current countershock is undoubtedly effective,[48] it is not without risk.[49 50] A pacing method of terminating recurrent supraventricular arrhythmias has obvious attraction because it can be repeated often and may be adapted for long term use. Failure to achieve sinus rhythm and the unwanted precipitation of atrial fibrillation are the two main disadvantages of overdrive atrial pacing for the treatment of paroxysmal atrial flutter. Though the incidence of atrial fibrillation can be minimised by limiting the duration of pacing, the pacing frequency, and the pacing energy, the successful conversion rate of this arrhythmia to sinus rhythm is also reduced by these limitations. Premedication of atrial flutter with disopyramide restores the effectiveness of limited overdrive atrial pacing without increasing the risk of atrial fibrillation.

References

1 Haft JI, Kosowsky BD, Lau SH, Stein E, Damato AN. Termination of atrial flutter by rapid electrical pacing of the atrium. *Am J Cardiol* 1967; **20:** 239–44.

2 Zeft HJ, Cobb FR, Waxman MB, Hunt NC, Morris JJ Jr. Right atrial stimulation in the treatment of atrial flutter. *Ann Intern Med* 1969; **70:** 447–56.

3 Gulotta SJ, Aronson AL. Cardioversion of atrial tachycardia and flutter by atrial stimulation. *Am J Cardiol* 1970; **26:** 262–9.

4 Pittman DE, Makar JS, Kooros KS, Joyner CR. Rapid atrial stimulation: successful method of conversion of atrial flutter and atrial tachycardia. *Am J Cardiol* 1973; **32:** 700–6.

5 Cheng TO. Atrial pacing: its diagnostic and therapeutic applications. *Prog Cardiovasc Dis* 1971; **14:** 230–47.

6 Cheng TO. Rapid atrial pacing in treatment of atrial flutter and atrial tachycardia (abstract). *Clin Res* 1971; **19:** 307.

7 Cheng TO. Rapid atrial pacing in conversion of atrial flutter (letter). *Am J Cardiol* 1973; **31:** 287.

8 Pittman DE, Gay TC, Patel II, Joyner CR. Termination of atrial flutter and atrial tachycardia with rapid atrial stimulation. *Angiology* 1975; **26:** 784–801.

9 Orlando J, Cassidy J, Aronow WS. High reversion of atrial flutter to sinus rhythm after atrial pacing in patients with pulmonary disease. *Chest* 1977; **71:** 580–2.

10 Waldo AL, MacLean WAH, Karp RB, Kouchoukos NT, James TN. Entrainment and interruption of atrial flutter with atrial pacing—studies in man following open heart surgery. *Circulation* 1977; **56:** 737–45.

11 Hunt NC, Cobb FR, Waxman MB, Zeft HJ, Peter RH, Morris JJ Jr. Conversion of supraventricular tachycardias with atrial stimulation—evidence for re-entry mechanism. *Circulation* 1968; **38:** 1060–5.

12 Puech P, Grolleau R, Latour H, Cabasson J, Robin JM, Baissus C. Traitement du flutter auriculaire par la stimulation auriculaire endocavitaire. *Arch Mal Coeur* 1973; **66:** 159–67.

13 Rosen KM, Sinno MZ, Gunnar RM, Rahimtoola SH. Failure of rapid atrial pacing in the conversion of atrial flutter. *Am J Cardiol* 1972; **29:** 524–8.

14 Camm AJ, Ward DE, Spurrell RAJ. Gaps in anterograde conduction in patients with the short PR interval, normal QRS complex syndrome. *Br Heart J* 1978; **40:** 1119–26.

15 Moe GK, Cohen W, Vick RL. Experimentally induced paroxysmal AV nodal tachycardia in the dog: a case report. *Am Heart J* 1963; **65:** 87–92.

16 Wit AL, Cranefield PF. Triggered activity in cardiac muscle fibers of the simian mitral valve *Circ Res* 1976; **38:** 85–98.

17 Massumi RA, Kistin AD, Tawakkol AA. Termination of reciprocating tachycardia by atrial stimulation. *Circulation* 1967; **36:** 637–43.

18 Durrer D, Schoo L, Schuilenburg RM, Wellens HJJ. The role of premature beats in the initiation and the termination of supraventricular tachycardia in the Wolff-Parkinson-White syndrome. *Circulation* 1967; **36:** 644–62.

19 Lister JW, Cohen LS, Bernstein WH, Samet P. Treatment of supraventricular tachycardias by rapid atrial stimulation. *Circulation* 1968; **38:** 1044–59.

20 Vergara GS, Hildner FJ, Schoenfeld CB, Javier RP, Cohen LS, Samet P. Conversion of supraventricular tachycardias with rapid atrial stimulation. *Circulation* 1972; **46:** 788–93.

21 Ward D, Camm J, Spurrell RAJ. The response of regular re-entrant supraventricular tachycardias to right heart stimulation. *Pace* 1979; **2:** 586–95.

22 Sasyniuk BI, Kus T. Cellular electrophysiologic changes induced by disopyramide phosphate in normal and infarcted hearts. *J Int Med Res* 1976; **4,** suppl 1: 20–5.

23 Sekiya A, Vaughan-Williams EM. A comparison of the antifibrillatory actions and effects of intracellular cardiac potentials of pronethalol, disopyramide and quinidine. *Br J Pharmacol* 1963; **21:** 473–81.

24 Spurrell RAJ, Thorburn C, Camm J, Sowton E, Deuchar DC. Effects of disopyramide on electrophysiological properties of specialized conduction system in man, and on accessory atrioventricular pathway in Wolff-Parkinson-White syndrome. *Br Heart J* 1975; **37:** 861–7.

25 Birkhead JS, Vaughan-Williams EM. Dual effect of disopyramide on atrial and atrioventricular conduction and refractory periods. *Br Heart J* 1977; **39:** 657–60.

26 Scherf D. The mechanism of flutter and fibrillation. *Am Heart J* 1966; **71:** 273–80.

27 Marques MG, Mota JCB, Nogueria RA. The mechanism of atrial flutter. *Cardiologia* 1962; **40:** 269–80.

28 Prinzmetal M, Goldman A, Gerlach E, Kennamer R. Nature of spontaneous auricular flutter in man. *JAMA* 1953; **153:** 553–5.

29 Lewis T, Drury AN, Iliescu CC. A demonstration of circus movement in clinical flutter of the auricles. *Heart* 1921; **8:** 341–55.

30 Rosenblueth A, Garcia Ramos J. Studies on flutter and fibrillation. 2. The influence of artificial obstacles on experimental auricular flutter. *Am Heart J* 1947; **33:** 677–84.

31 Rytand DA. The circus movement (entrapped circuit wave) hypothesis and atrial flutter. *Ann Intern Med* 1966; **65:** 125–59.

32 Gough W, Dreifus LS, de Azevado IM, Katz MR. Refractoriness of cardiac tissue. *Cardiovasc Clin* 1974; **6 1:** 87–97.

33 Luoma PV, Kujala PA, Juustila HJ, Takkunen JT. Efficacy of intravenous disopyramide in the termination of supraventricular arrhythmias. *J Clin Pharmacol* 1978; **18:** 293–301.

34 Vandenbosch R, Lisin N, Andriange M, Gach J, Carlier J. Experimentation clinique du disopyramide administre par voie intravineuse. *Acta Cardiol (Brux)* 1975; **30:** 267–78.

35 Deano DA, Wu D, Mautner RK, Sherman RH, Ehsani AE, Rosen KM. The antiarrhythmic efficacy of intravenous therapy with disopyramide phosphate. *Chest* 1977; **71:** 597–606.

36 Camm J, Ward D, Spurrell RAJ. The effect of intravenous disopyramide phosphate on recurrent paroxysmal tachycardias. *Br J Clin Pharmacol* 1979; **8:** 441–9.

37 Hill I. Fallacies in the clinical evaluation of antiarrhythmic drugs. In: Sandoe E, Flensted-Jensen E, Olesen KH, eds. *Symposium on cardiac arrhythmias.* Södertälje: AB Astra, 1970: 473–7.

38 Jequier R, Deraedt R, Plongeron R, Vannier B. Pharmacologie et toxicologie du disopyramide. Farmacologia e tossicologia della disopiramide. *Minerva Med* 1970; **61,** suppl 71: 7–10.

39 Baines MW, Davies JE, Kellett DN, Munt PL. Some pharmacological effects of disopyramide and a metabolite. *J Int Med Res* 1976; **4,** suppl 1: 5–7.

40 Lewis T. *The mechanism and graphic registration of the heart beat.* 3rd ed. London: Shaw & Sons, 1925: 359–60.

41 Acierno LJ, Gubner R. Utility and limitations of intravenous quinidine in arrhythmias. *Am Heart J* 1951; **41:** 733–41.

42 Brown BB. A study of factors related to effects of quinidine in experimental auricular flutter. *Circulation* 1952; **5:** 864–9.

43 Miller G, Weinberg SL, Pick A. The effect of procaine amide (Pronestyl) in clinical auricular fibrillation and flutter. *Circulation* 1952; **6:** 41–50.

44 Wyndham CR, Wu D, Denes P, Sugarman D, Levitsky S, Rosen KM. Self-initiated conversion of paroxysmal atrial flutter utilizing a radio-frequency pacemaker. *Am J Cardiol* 1978; **41:** 1119–22.

45 Lewis T. *The mechanism and graphic registration of the heart beat.* 3rd ed. London: Shaw & Sons, 1925: 322.

46 Schamroth L, Krikler DM, Garrett C. Immediate effects of intravenous verapamil in cardiac arrhythmias. *Br Med J* 1972; **1:** 660–2.

47 Gianelly R, Griffin JR, Harrison DC. Propranolol in the treatment and prevention of cardiac arrhythmias. *Ann Intern Med* 1967; **66:** 667–76.

48 Castellanos A Jr, Lemberg L, Gosselin A, Fonseca EJ. Evaluation of countershock treatment of atrial flutter. *Arch Intern Med* 1965; **115:** 426–33.

49 Lown B, Kleiger R, Williams J. Cardioversion and digitalis drugs; changed threshold to electric shock in digitalized animals. *Circ Res* 1965; **17:** 519–31.

50 Rabbino MD, Likoff W, Dreifus LS. Complications and limitations of direct current countershock. *JAMA* 1964; **190:** 417–20.

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Br Heart J 1980; **44:** 248–53

Detection of late arrhythmia and conduction disturbance after correction of tetralogy of Fallot

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SUMMARY The electrocardiographic conduction disturbances were evaluated retrospectively, in relation to prognosis, in 196 patients who underwent correction of tetralogy of Fallot. The follow-up was one to 20 years (mean 10). After surgery complete right bundle-branch block occurred in 187 patients (95%), right bundle-branch block and left axis deviation in 17 patients (9%), and progressive conduction defects, either left axis deviation or right bundle-branch block, developed during follow-up in 21 patients (11%). Nine patients (4·6%) died suddenly and two patients developed complete heart block late after the operation. Though late sudden death or complete heart block occurred in 19 per cent of patients with progressive conduction defects as opposed to 4 per cent of the group with stable conduction defects, the difference was not significant.

Twenty-four hour ambulatory electrocardiographic monitoring was performed in 74 patients; 41 per cent had significant (Lown grade 2, 3, or 4) ventricular arrhythmias. The incidence of ventricular arrhythmia in the group with progressive conduction defects (80%) was significantly higher than in the group with stable conduction defects (30%). As occult arrhythmia may be the cause of sudden death, it is important to identify these patients.

Late sudden death has been reported after surgical correction of tetralogy of Fallot in up to 3·4 per cent of patients.[1] Both the cause of these deaths and the prognostic significance of preoperative and postoperative conduction disturbances remain controversial. Right bundle-branch block is the commonest conduction disturbance: Kulbertus *et al.*[2] first described the occurrence of right bundle-branch block and left anterior hemiblock after correction of tetralogy of Fallot, and suggested that patients with this electrocardiographic finding might have a poor prognosis. Wolff *et al.*[3] reported a significantly increased incidence of late complete heart block and sudden death in this group; others, however, have suggested a benign prognosis.[4 5] Ventricular arrhythmias have also been reported after correction of tetralogy of Fallot and it has been suggested that they may lead to sudden death.[1 6–8]

The purpose of this study was to determine the nature and prevalence of arrhythmia after correction of tetralogy of Fallot. Retrospective analysis was also performed to correlate the arrhythmias detected with postoperative conduction disturbances.

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Patients and methods

The electrocardiograms of 196 consecutive patients, 114 male and 82 female, who underwent correction of tetralogy of Fallot at the Hammersmith Hospital between 1959 and 1971 were reviewed. Patients who died within one month of operation were excluded from the study. The age of patients at the time of corrective surgery was 3 to 20 years (mean 11). Thirty-eight patients (19%) had previously undergone a Brock operation and 74 (37%) had had a shunt procedure. The duration of follow-up was one to 20 years (mean 10).

The electrocardiograms were routine 12 lead tracings, and were recorded preoperatively (one to two days before surgery), postoperatively, and serially during the follow-up period. They were analysed for the presence of arrhythmias, conduction disturbances, and mean frontal QRS axis change. Right bundle-branch block was diagnosed when the QRS interval in the right praecordial leads exceeded 120 milliseconds with terminal conduction delay. Incomplete right bundle-branch block was defined as a QRS duration of less than 120 milliseconds with terminal conduction delay. Left axis deviation was considered present when the frontal plane QRS axis was between −30° and −120°.

Preoperative and perioperative pulmonary artery, right ventricular, and left ventricular pressures were available in 180 (92%) patients: 72 patients (37%) underwent cardiac catheterisation in the follow-up period.

Twenty-four hour out-patient ambulatory electrocardiographic monitoring was performed on 74 patients using the Oxford Medilog cassette recording system. These patients were being followed up at the Hammersmith Hospital or other centres where ambulatory monitoring facilities were available. No other selection criteria were employed. The recordings were analysed by one of the authors using a Reynolds High Speed Pathfinder analyser and they were reviewed by a second physician. The ventricular arrhythmias found were graded using a modification of the Lown criteria.[9] The following categories were defined: grade 0, no ventricular extrasystoles in 24 hours; grade 1, occasional ventricular extrasystoles, but no more than 30 in any hour of monitoring; grade 2, more than 30 ventricular extrasystoles in any hour of monitoring; grade 3, multiform ventricular extrasystoles; grade 4a, couplets (two consecutive ventricular extrasystoles); grade 4b, ventricular tachycardia (three or more ventricular extrasystoles in succession).

STATISTICAL ANALYSIS

The Fisher exact test was used, where appropriate, to assess statistical significance.

Results

ELECTROCARDIOGRAM

Table 1 summarises the conduction patterns found on the preoperative, postoperative, and most recent follow-up electrocardiogram. Complete right bundle-branch block occurred in 95 per cent of patients after operation, and postoperative right bundle-branch block and left axis deviation in 9 per cent of patients. During the follow-up period five patients (2·5%) developed right bundle-branch block and 16 patients (8%) developed progressive shift in QRS axis to left axis deviation. These late conduction defects occurred between six months and six years after operation. From the postoperative and follow-up electrocardiograms, three groups of patients were defined: (a) postoperative right bundle-branch block with normal axis or right axis deviation; (b) postoperative right bundle-branch block and left axis deviation; (c) progressive conduction defects, either progressive left axis shift or the development of right bundle-branch block during follow-up.

Table 1 *Conduction defects on preoperative, postoperative, and follow-up electrocardiograms*

Conduction pattern	*Preoperative*		*Postoperative*		*Follow-up*	
	No. of patients	(%)	*No. of patients*	(%)	*No. of patients*	(%)
Normal	170	(87)	7	(4)	2	(1)
Incomplete RBBB	22	(11)	2	(1)	2	(1)
Complete RBBB	4	(2)	187*	(95)	192	(98)
RBBB + LAD	0	(0)	17	(9)	33	(17)

RBBB, right bundle-branch block; LAD, left axis deviation.
* Includes the 17 patients who also had left axis deviation.

POSTOPERATIVE ARRHYTHMIAS

Table 2 summarises the perioperative arrhythmias detected in relation to the underlying electrocardiographic conduction defects. Perioperative transient complete heart block occurred in nine patients (5%), one with postoperative right bundle-branch block and left axis deviation, and one with progressive left axis shift during follow-up.

LATE ARRHYTHMIAS

First degree atrioventricular block was seen in 20 patients (10%) during follow-up. One of these patients had left axis deviation postoperatively and three had progressive late left axis deviation. Late complete heart block was uncommon, occurring in only two patients. Both of these patients had progressive late left axis deviation and one had had transient perioperative complete heart block. Ventricular extrasystoles were noted in 29 patients (15%) on routine electrocardiograms.

MORTALITY

Fifteen patients died during the follow-up period. Four of the deaths were a result of infective endocarditis and two patients died at reoperation. Sudden death during follow-up, from documented or suspected arrhythmia, occurred in nine patients (4·6%). The interval between surgery and death was two to 15 years (mean 5·5). Five of the patients who died suddenly were asymptomatic, while three had complained of syncopal episodes, and one of palpitation. None of these patients had undergone ambulatory electrocardiographic monitoring. Their conduction defects and arrhythmia documentation are shown in Table 3. Postoperatively, eight patients had right bundle-branch block and one patient had additional left axis deviation. During follow-up, there was progressive change in the electrocardiogram in two patients, one developing

Table 2 *Frequency of perioperative arrhythmias related to electrocardiographic conduction defects*

Conduction defect	*Total patients*	*First degree AV block*	*Complete heart block*	*Nodal rhythm*	*Ventricular extrasystoles*
Total group	196	18 (9%)	9 (5%)	10 (5%)	21 (11%)
RBBB	158	12 (8%)	7 (4%)	9 (6%)	17 (11%)
RBBB+LAD	17	4 (23%)	1 (6%)	0 (0%)	3 (18%)
Progressive conduction defect	21	2 (10%)	1 (5%)	1 (5%)	1 (5%)

LAD, left axis deviation; AV, atrioventricular.

left axis deviation and the other right bundle-branch block.

Postoperative complete heart block and ventricular arrhythmia were not found in any of the patients who died suddenly. During follow-up, one patient had supraventricular tachycardia and another frequent ventricular extrasystoles, but no cases of complete heart block or bradycardia were documented.

AMBULATORY MONITORING

Supraventricular arrhythmias

Thirty-eight patients (56%) had atrial extrasystoles recorded on the 24-hour electrocardiogram. The total number of atrial extrasystoles ranged from one to 5184 in 24 hours. Only four patients (5%) had more than 1000 atrial extrasystoles in 24 hours, and two of these patients belonged to the group with progressive conduction disorders. A further four patients (5%) had paroxysmal supraventricular tachycardia.

Thirteen patients (18%) had evidence of sinus node dysfunction, with either periods of sinus arrest for longer than two seconds, sinus bradycardia less than 35 beats per minute, or sinuatrial block. Three of these 13 patients had progressive left axis shift on serial electrocardiograms.

Table 3 *Arrhythmias and conduction defects in patients who died suddenly*

Case no.	*Postoperative conduction defect*	*Follow-up conduction defect*	*Postoperative arrhythmia*	*Late arrhythmia*
1	RBBB	RBBB	—	—
2	RBBB	RBBB	—	—
3	RBBB	RBBB	—	Supraventricular tachycardia
4	RBBB	RBBB	—	—
5	RBBB	RBBB+LAD	—	—
6	RBBB	RBBB	—	Ventricular extrasystoles
7*	RBBB	RBBB	—	—
8	RBBB+LAD	RBBB+LAD	—	—
9	Normal	RBBB	Junctional tachycardia	—

LAD, left axis deviation; RBBB, right bundle-branch block.

*Operation performed at The Hospital for Sick Children, Great Ormond Street.

Atrioventricular block

The incidence of atrioventricular block during ambulatory monitoring is shown on Table 4. First degree heart block was noted throughout the 24-hour period in three patients and occurred intermittently in a further three cases. Five of these six patients had right bundle-branch block with a normal QRS axis, and the remaining patient had progressive left axis deviation during follow-up. Second degree heart block and complete heart block were uncommon findings: transient atrioventricular dissociation, with a ventricular rate of 50 to 60/minute, occurred in two patients, and both had right bundle-branch block and a normal QRS axis.

Table 4 *Atrioventricular block detected during ambulatory monitoring in 74 patients*

Heart block	*Conduction defect on electrocardiogram*		
	RBBB no. = 55	*RBBB+LAD no. = 4*	*PCD no. = 15*
Intermittent 1° AVB	2	0	1
Stable 1° AVB	3	0	0
2° AVB	2	0	0
3° AVB	2	0	0

AVB, atrioventricular block; PCD, progressive conduction defect; LAD, left axis deviation.

Ventricular arrhythmias

Fifty-seven patients (77%) had ventricular extrasystoles, ranging from one to 10 191 per 24 hours. Seventeen patients (23%) had over 500 ventricular extrasystoles in 24 hours, 15 patients (20%) had multiform ventricular extrasystoles, and 13 patients (18%) had pairs of ventricular extrasystoles (couplets). Ventricular arrhythmias, of Lown grade 2 or greater, were found in 30 patients (41%). Ventricular tachycardia (grade 4b) was not detected in any of the patients during 24-hour monitoring.

Table 5 shows the frequency and grade of ventricular ectopic activity detected during 24-hour monitoring in relation to the conduction pattern on the resting electrocardiogram. The incidence of grade 2, 3, or 4 ventricular arrhythmias in the group

Table 5 *Frequency and grade of ventricular ectopic activity during 24-hour monitoring in relation to electrocardiographic conduction pattern*

Conduction defect	*No. of patients*	*Per cent of patients with ventricular extrasystoles*	*Highest grade of ventricular extrasystoles during 24 hours (%)*						*Per cent of patients with ventricular extrasystoles*			
			0	*1*	*2*	*3*	*4a*	*4b*	*Thirty* in any hour*	*Total* 500 to 1000*	*Total* > 1000*	*Grade 2, 3, or 4*
RBBB	55	76	24	46	2	14	14	0	13	11	5	30
RBBB + postop LAD	4	50	50	25	0	0	25	0	25	0	25	25
PCD	15	87	13	7	20	33	27	0	33	20	27	80
Total group	74	77	23	36	6	17	18	0	18	12	11	41

PCD, progressive conduction defect; LAD, left axis deviation.
* These three categories and the ventricular extrasystole grades are not mutually exclusive.

of patients with progressive conduction defects was 80 per cent. This is significantly higher than the incidence found in the group with right bundle-branch block and no axis shift during follow-up ($p < 0{\cdot}01$).

Symptoms, surgical technique, and postoperative haemodynamic data (in particular the presence of a residual ventricular septal defect or right ventricular outflow obstruction) were analysed. We were, however, unable to establish any symptom, haemodynamic measurement, or surgical factor as a predictor of conduction defects, late arrhythmias, or late sudden death.

Discussion

The overall incidence of late sudden death during a mean follow-up of 10 years was 4·6 per cent. This compares with reported incidences of 2·9 per cent[7] and 3·4 per cent[1] over a similar period. Previous reports have attempted to identify risk factors for sudden death and to determine the antecedent mechanism. Several authors have suggested that the presence of right bundle-branch block and left axis deviation after correction of tetralogy of Fallot implies a poor long-term prognosis.[2 3] Wolff *et al.*[3] reported a series of 24 patients with right bundle-branch block and left axis deviation in which the incidence of sudden death was 12·5 per cent. The significance of this conduction disturbance, however, has been the subject of controversy. Cairns *et al.*[4] reported no sudden deaths among 31 patients with postoperative right bundle-branch block and left axis deviation over a mean follow-up of 27 months. A favourable prognosis has also been found by Downing *et al.*[5] and Steeg *et al.*[10] In our study we are also unable to associate a poor prognosis with this conduction disturbance as only one of 17 patients with postoperative right bundle-branch block and left axis deviation has died suddenly. An important finding, however, was a group of 21 patients (11%) with evidence of progression of conduction disturbance during long-term follow-up. These patients had either normal conduction or right bundle-branch block alone postoperatively, but developed left axis deviation or new right bundle-branch block between six months and six years after surgery. Though the difference was not statistically significant, sudden death or complete heart block occurred in 19 per cent of the patients with progressive conduction defects and in only 4 per cent with stable conduction pattern.

The disparity in reported prognosis for patients with postoperative right bundle-branch block and left axis deviation may result from the failure of the scalar electrocardiogram to distinguish between central and peripheral damage to the conducting system. Injury to the central portion of the right bundle may occur as a result of closure of the ventricular septal defect,[11] while right bundle-branch block may result from damage to the distal right bundle caused by right ventriculotomy.[12] Horowitz *et al.*[13] using epicardial activation mapping, found that right bundle-branch block appeared after infundibular resection during transatrial repair of tetralogy of Fallot. Additional left axis deviation need not necessarily imply block of the anterior fascicle of the left bundle-branch.[14 15] Thus, patients with right bundle-branch block and left axis deviation are not likely to represent a homogeneous group. The anatomical location of the lesions in the patients with progressive conduction defects remains to be clarified by electrophysiological and pathological studies.

There is still debate about the nature of the arrhythmia responsible for late sudden death after correction of tetralogy of Fallot. Wolff *et al.*[3] speculated that sudden death associated with right bundle-branch block and left axis deviation results from subsequent complete heart block. Moss *et al.*[16] also reported late complete heart block after correction of tetralogy of Fallot and related its occurrence to perioperative complete heart block. Intracardiac electrophysiological studies have been performed to identify patients at risk from complete heart block. Gillette *et al.*[6] found a prolonged HV interval in only one of eight patients with postoperative right bundle-branch block and left axis deviation, and they were unable to correlate either first degree block, prolonged AH or HV intervals with late complete heart block, or a poor prognosis. In our series there were only two cases of late complete heart block; both patients had progressive left axis deviation during follow-up with a normal postoperative QRS axis. Transient perioperative complete heart block occurred in 10 patients. Only one of these developed late complete heart block, and one other has died. Twenty-four hour monitoring has not disclosed a high incidence of unsuspected heart block associated with any electrocardiographic conduction defect.

Ventricular arrhythmia is an alternative mechanism for sudden death after correction of tetralogy of Fallot. Gillette *et al.*[6] reported late sudden death in three of nine patients with ventricular extrasystoles on the resting electrocardiogram, none of whom had significant conduction disturbance during intracardiac electrophysiological study. Garson *et al.*[1] in a series of 233 patients found ventricular extrasystoles on the electrocardiograms of all eight patients who died suddenly, with no evidence of complete heart block. James *et al.*,[8] Quattlebaum *et al.*,[7] and Rosing *et al.*[17] all considered ventricular arrhythmias to be a more important cause of sudden death than heart block. Our results have shown a high incidence (41%) of significant ventricular arrhythmias (Lown grade 2 or above) on ambulatory monitoring. This incidence is considerably greater than that found in studies of comparable subjects without heart disease.[18] These ventricular arrhythmias were significantly increased among patients with evidence of progressive conduction defects. Ventricular extrasystoles, in the presence of conduction block, may be particularly significant because of a greater potential for re-entry arrhythmias. Even ventricular extrasystoles which have features normally considered benign may be important and in Quattlebaum's series[7] the ventricular extrasystoles associated with sudden death were unifocal, with late coupling. Garson *et al.*[1] were able to correlate the occurrence of ventricular arrhythmias and sudden death with a raised right ventricular systolic pressure. We were, however, unable to relate the presence of arrhythmias or late sudden death to surgical technique or to any residual postoperative haemodynamic abnormality.

We cannot link the presence of ventricular arrhythmia with sudden death as none of our patients who underwent 24-hour monitoring has died. Several different mechanisms are probably responsible for late sudden death after correction of tetralogy of Fallot. Our results disclosed a high incidence of serious ventricular arrhythmia, particularly in patients with progressive conduction disease. As occult arrhythmia may be the cause of sudden death in tetralogy of Fallot, it is important to detect these patients; appropriate treatment remains to be defined.

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References

1. Garson A Jr, Nihill MR, McNamara DG, Cooley DA. Status of the adult and adolescent after repair of tetralogy of Fallot. *Circulation* 1979; **59:** 1232–40.
2. Kulbertus HE, Coyne JJ, Hallidie-Smith KA. Conduction disturbances before and after surgical closure of ventricular septal defect. *Am Heart J* 1969; **77:** 123–31.
3. Wolff GS, Rowland TW, Ellison RC. Surgically induced right bundle-branch block with left anterior hemiblock. An ominous sign in postoperative tetralogy of Fallot. *Circulation* 1972; **46:** 587–95.
4. Cairns JA, Dobell ARC, Gibbons JE, Tessler I. Prognosis of right bundle branch-block and left anterior hemiblock after intracardial repair of tetralogy of Fallot. *Am Heart J* 1975; **90:** 549–54.
5. Downing JW Jr, Kaplan S, Bove KE. Postsurgical left anterior hemiblock and right bundle-branch block. *Br Heart J* 1972; **34:** 263–70.
6. Gillette PC, Yeoman MA, Mullins CE, McNamara DG. Sudden death after repair of tetralogy of Fallot. Electrocardiographic and electrophysiologic abnormalities. *Circulation* 1977; **56:** 566–71.
7. Quattlebaum TG, Varghese PJ, Neill CA, Donaghoo JS. Sudden death among postoperative patients with tetralogy of Fallot. A follow up study of 243 patients for an average of 12 years. *Circulation* 1976; **54:** 289–93.
8. James FW, Kaplan S, Chou TC. Unexpected cardiac arrest in patients after surgical correction of tetralogy of Fallot. *Circulation* 1975; **52:** 691–5.
9. Ryan M, Lown B, Horn H. Comparison of ventricular ectopic activity during 24-hour monitoring and exercise testing in patients with coronary heart disease. *N Engl J Med* 1975; **292:** 224–9.
10. Steeg CN, Krongrad E, Davachi F, Bowman FO Jr, Malm JR, Gersony WM. Postoperative left anterior hemiblock and right bundle branch block following repair of tetralogy of Fallot: clinical and etiologic consideration. *Circulation* 1975; **51:** 1026–9.

11 Titus JL, Daugherty GW, Kirklin JW, Edwards JE. Lesion of the atrioventricular conduction system after repair of ventricular septal defect: relation to heart block. *Circulation* 1963; **28:** 82–8.
12 Gelband H, Waldo AL, Kaiser GA, Bowman FO Jr, Malm JR, Hoffman BF. Etiology of right bundle-branch block in patients undergoing total correction of tetralogy of Fallot. *Circulation* 1971; **44:** 1022–33.
13 Horowitz LN, Simson MB, Spear JF, *et al.* The mechanism of apparent right bundle branch block after transatrial repair of tetralogy of Fallot. *Circulation* 1979; **59:** 1241–52.
14 Krongrad E, Rosen MR, Merker C, Hoffman BF. Creation of counterclockwise superiorly orientated frontal plane loops (CCW-SOFPL) in isolated blood perfused canine hearts (abstract). *Pediatr Res* 1973; **7:** 300.
15 Watt TB Jr, Pruitt RD. Focal lesions in the canine bundle of His: their effects on ventricular excitation. *Circ Res* 1972; **31:** 531–45.
16 Moss AJ, Klyman G, Emmanouilides GC. Late onset complete heart block. *Am J Cardiol* 1972; **30:** 884–7.
17 Rosing DR, Borer JS, Kent KM, *et al.* Long-term hemodynamic and electrocardiographic assessment following operative repair of tetralogy of Fallot. *Circulation* 1978; **58,** suppl I: 209–17.
18 Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. *Am J Cardiol* 1977; **39:** 390–5.

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Haemodynamic changes induced by prostacyclin in man

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SUMMARY Intra-arterial or intravenous infusion of prostacyclin at three dose levels (2, 5, and 10 ng/kg per min) in 10 subjects without evidence of coronary heart disease or cardiac failure, led to a distinct fall in peripheral and total pulmonary vascular resistances. This was accompanied by a drop in intra-arterial blood pressure, and the acceleration of heart rate. Stroke volume, cardiac output, mean right atrial pressure, and left ventricular end-diastolic pressure showed no significant changes. Except for sporadic headache no side effects occurred. Prostacyclin appears to act predominantly on resistance vessels. The haemodynamic effects produced by prostacyclin in man might be of clinical interest in the treatment of conditions associated with a significant rise in vascular resistance.

Prostacyclin (PGI_2) is a metabolite of arachidonic acid, generated by the arterial walls[1, 2] and secreted into the circulation by the lungs.[3] In man, it blocks platelet aggregation, disperses circulating platelet aggregates, and causes vasodilatation.[4] It might well be that prostacyclin shields arteries against mural thrombosis and stops development of atherosclerosis.[5]

The remarkable properties of prostacyclin have been found beneficial in treating advanced arteriosclerosis obliterans.[6] They could also be useful in the management of atherosclerotic heart disease provided more was known about the haemodynamic effects of prostaglandin in man.

Patients and methods

The study included 10 men, aged 34 to 65 years, who underwent treatment with prostacyclin because of peripheral arterial disease. Arteriosclerosis obliterans was diagnosed in seven of them, and thrombangiitis in the remaining three. The diagnosis was based on typical history, clinical examination, and in each case it was confirmed by angiography. There was no evidence of either coronary heart disease or cardiac failure.

The patients had not received any drugs for a period of about a week preceding the infusion. The study was carried out in the intensive care unit under continuous electrocardiographic monitoring.

Cooled solution of lyophilised sodium salt of prostacyclin (synthesised by The Upjohn Company, Kalamazoo, Michigan, USA, and formulated by The Wellcome Research Laboratories, Beckenham, England) in glycine buffer pH 10·5 was infused during 72 hours. Six patients (cases 1, 2, 3, 7, 9, and 10) received infusions into the femoral artery of the affected limb, four others (cases 4, 5, 6, and 8) into the subclavian vein. The initial dose of 2 ng/kg per min was stepped up, first to 5 ng/kg per min and then to 10 ng/kg per min.

Right heart catheterisation was carried out with a 7F Swan-Ganz flow-directed thermodilution catheter, inserted through a cutdown in an ante-

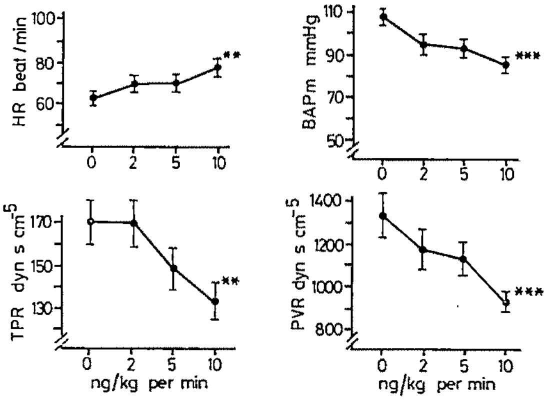

Fig. *The effects of prostacyclin infusion on heart rate (HR), mean brachial artery pressure (BAPm), total pulmonary resistance (TPR), and peripheral vascular resistance (PVR).*

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Table 1 *Changes in heart rate (HR), mean brachial artery pressure (BAPm), cardiac index (CI), stroke volume index (SVI), pulmonary end-diastolic pressure (PAEDP), and mean right atrial pressure (RAPm) after infusion of 5 and 10 ng/kg per min PGI_2*

Case no.	*Age (y)*	*HR (beat/min) PGI_2 (ng/kg per min)*			*BAPm (mmHg) PGI_2 (ng/kg per min)*			*CI (l/min per m^2) PGI_2 (ng/kg per min)*			*SVI (ml/beat per m^2) PGI_2 (ng/kg per min)*			*PAEDP (mmHg) PGI_2 (ng/kg per min)*			*RAPm (mmHg) PGI_2 (ng/kg per min)*		
		0	*5*	*10*	*0*	*5*	*10*	*0*	*5*	*10*	*0*	*5*	*10*	*0*	*5*	*10*	*0*	*5*	*10*
1	59	78	98	93	130	124	92	3·18	2·79	3·66	40·8	28·5	39·5	11	8	10	0	—	1
2	48	58	70	73	105	100	71	3·06	3·35	3·03	52·8	47·8	37·9	7	6	8	2	—	3
3	49	58	77	88	120	100	100	2·66	3·65	3·80	45·9	47·4	40·0	7	4	9	2	1	4
4	70	56	57	72	130	110	100	3·20	3·24	4·09	55·2	57·9	73·1	10	8	4	3	2	3
5	48	61	73	85	100	90	90	3·25	3·57	4·07	52·7	48·6	47·6	12	10	8	6	0	4
6	47	44	56	66	110	90	90	3·52	3·75	4·85	80·0	67·1	73·5	12	14	13	6	8	8
7	50	71	58	59	95	74	75	4·90	4·16	4·10	68·8	70·5	70·6	11	8	8	3	3	3
8	64	73	76	86	100	80	77	3·03	3·18	3·45	41·2	41·8	38·4	8	9	8	2	5	−2
9	44	71	67	68	101	90	83	4·97	4·40	4·55	69·7	66·4	65·5	10	10	9	2	2	1
10	34	65	82	97	90	90	85	4·23	4·00	4·82	65·1	48·8	49·7	8	5	7	3	4	3
Mean	51·9	63·5	71·4	78·7*	108·1	94·8	86·3†	3·6	3·6	4·0	57·2	52·4	53·5	9·7	8·2	8·3	2·8	2·7	2·7
±SEM		±3·1	±4·1	±4·0	±4·4	±4·5	±3·1	±0·2	±0·1	±0·1	±4·1	±4·1	±4·8	±0·6	±0·9	±0·7	±0·6	±0·8	±0·8

*$p < 0·02$. †$p < 0·005$.

Table 2 *Changes in mean pulmonary artery pressure (PAm), pulmonary wedge resistance (PWR), total pulmonary resistance (TPR), peripheral vascular resistance (PVR), and left ventricular stroke work index (LVSWI) after infusion of 5 and 10 ng/kg per min PGI_2*

Case no.	*PAm (mmHg) PGI_2 (ng/kg per min)*			*PWR (dynes s cm^{-5}) PGI_2 (ng/kg per min)*			*TPR (dynes s cm^{-5}) PGI_2 (ng/kg per min)*			*PVR (dynes s cm^{-5}) PGI_2 (ng/kg per min)*			*LVSWI (g m/m^2) PGI_2 (ng/kg per min)*		
	0	*5*	*10*	*0*	*5*	*10*	*0*	*5*	*10*	*0*	*5*	*10*	*0*	*5*	*10*
1	16	13	16	49·8	—	6·4	207	184	162	1621	1733	1000	66	45	38
2	11	13	12	92·0	98·1	62·2	161	168	173	1611	1416	1204	70	61	29
3	12	9	14	139·3	56·0	86·2	185	100	150	1858	1121	1077	67	58	49
4	16	8	12	140·8	52·9	31·4	241	158	83	1743	1455	1048	90	80	96
5	16	15	13	92·2	55·9	68·6	196	167	127	1229	1007	882	63	53	53
6	16	18	17	34·8	43·6	38·0	186	196	143	1279	981	760	106	126	77
7	15	13	12	61·1	84·0	48·7	153	156	146	968	888	913	78	63	64
8	10	11	10	109·8	143·4	138·4	137	144	129	1373	1046	932	51	40	36
9	15	14	13	59·1	85·0	75·5	126	132	112	853	850	781	86	72	65
10	11	9	13	48·1	56·0	63·3	105	86	101	866	916	718	72	56	52
Mean	13·8	12·3	13·2	82·7	74·9	61·8	169·9	149·3	132·9*	1340	1141	931†	75·2	65·7	56†
±SEM	±0·8	±1·2	±0·7	±12	±10·5	±11·2	±12·9	±11·0	±28·0	±115	±92	±48	±4·9	±7·6	±6·4

*$p < 0·02$. †$p < 0·005$.

cubital vein. The catheter was connected to a 756 pressure transducer and 863 amplifier of Mingograf 82 recorder (Elema-Siemens) from which measurements of right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures were made. Cardiac output was measured using the thermodilution technique in triplicate, and the mean was calculated. Arterial blood pressure was determined continuously through a cannula inserted into the left brachial artery.

Cardiac output, stroke volume, and both left and right ventricular stroke work were expressed as indices by dividing by body surface. In calculating the left ventricular stroke work index pulmonary artery end-diastolic pressure was used instead of left ventricular end-diastolic pressure. Peripheral vascular resistance, total pulmonary resistance, and pulmonary wedge resistance were calculated by the standard formulae.

Simultaneously, external systolic time intervals were measured from the carotid artery and praecordial phonocardiogram and electrocardiogram. The differences between time intervals after correction for standard heart rate were compared.[7] Left ventricular dP/dt_{max} was calculated by the indirect method[8] using the following formula for mean electromechanical $\Delta p/\Delta t$: BPd-PAEDP/PEP, where BPd is diastolic blood pressure in the brachial artery, PAEDP is pulmonary artery end-diastolic pressure, and PEP is pre-ejection period.

Additionally, in three of 10 patients both resting and hyperaemic calf muscle blood flows in the affected limbs were measured according to Lassen *et al.*, as described previously,[6] and expressed in ml per min per 100 g.

Student's t test for unpaired data was used in statistical evaluation.

Results

In all 10 patients the initial haemodynamic values studied were within the normal range, except for decreased resting and hyperaemic muscle blood flow. The changes in certain haemodynamic indices appeared early during infusion of the lowest dose of PGI_2. These changes became more pronounced with the increase in dose of the infused hormone. PGI_2 at a dose of 10 ng/kg per min caused a distinct fall in pulmonary vascular resistance from 1340 to 932 dynes s cm^{-5} ($p<0{\cdot}01$). At the same time arterial blood pressure (mean, systolic, and diastolic) fell on average by 20 per cent. Heart rate rose from mean 63/minute to 79/minute ($p<0{\cdot}01$), while left ventricular stroke work index declined from 75 to 56 g m/m^2 ($p<0{\cdot}05$). There was a mild, insignificant decrease by 12 per cent in pulmonary wedge resistance. Total pulmonary resistance, however, fell significantly ($p<0{\cdot}05$) from mean 170 to 133 dynes s cm^{-5}. The following indices remained unaffected by the administration of PGI_2: cardiac output, cardiac index, stroke volume index, pulmonary artery end-diastolic pressure, and right atrial pressure. Mean electromechanical $\Delta p/\Delta t$ showed no changes during infusion of 2 and 5 ng/kg per min PGI_2, and fell during the administration of 10 ng/kg per min PGI_2. Systolic time intervals remained unchanged throughout PGI_2 infusion. Hyperaemic muscle blood flow increased in the affected limbs (from $3{\cdot}3\pm0{\cdot}7$ to $11{\cdot}9\pm3{\cdot}0$ ml/min per 100 g at 10 ng/kg per min PGI_2).

The route of administration of PGI_2 did not seem to affect the haemodynamic indices studied, which showed similar changes in patients receiving intra-arterial or intravenous infusions. In some patients prolonged infusion of high doses of PGI_2 caused headache or pain in the leg. Decrease in dose resulted in rapid disappearance of these symptoms. No other side effects occurred.

Discussion

Vasodilatory properties of PGI_2 described in man previously[8] explain several of the haemodynamic findings reported here. Of these, a pronounced fall in vascular resistance was the most striking phenomenon. This fall included pulmonary vascular resistance and total pulmonary resistance. It occurred even during infusion of the lowest dose of PGI_2, progressed in a dose-dependent manner, and was accompanied by a distinct rise in muscle blood flow. These effects were most striking in the subjects with basic pulmonary vascular resistance values close to the upper limit of the normal range. Thus, in four patients with basic values between 1500 to 1800 dynes s cm^{-5} pulmonary vascular resistance fell on average by 40 per cent, while in the remaining six patients (basic values below 1500 dynes s cm^{-5}) it declined by only 24 per cent.

A similar dose-dependent fall in pulmonary vascular resistance after PGI_2 injection was reported recently in several experimental animal models.[10 11] Man, however, appears to be more sensitive to PGI_2 than the animals studied. Infusion of five to 10 times lower concentrations of prostacyclin to man than to the animals[10 12 13] resulted in a similar fall in pulmonary vascular resistance in both groups.

In comparison to prostaglandin E_1 (PGE_1) prostacyclin has a stronger vasodilatatory action in man. Doses of PGE_1[14] at least twice as high were necessary to reduce pulmonary vascular resistance to the range similar to that reported here. Prostacyclin was also better tolerated than PGE_1. We have not observed abdominal cramps or back pain, which were frequently recorded in subjects receiving PGE_1, and which had necessitated interruption of the infusion.[15]

Although PGI_2 depressed significantly total pulmonary resistance, its effects on the pulmonary bed were less pronounced than those on peripheral vascular resistance. Thus, during the administration of PGI_2 at a dose of 10 ng/kg per min pulmonary wedge resistance fell by 12·5 per cent, total pulmonary resistance by 21·7 per cent, and peripheral vascular resistance by 30·4 per cent—in comparison with initial values. Similarly, Kadowitz *et al.*[16] obtained a more pronounced fall in systemic than pulmonary vascular resistance in dogs receiving PGI_2. Though neither in animals nor in men were these differences of striking magnitude, they nevertheless might suggest that the two vascular beds vary in sensitivity to PGI_2. This observation seems interesting, since the sensitivity to the vasodilatating action of prostaglandins varies between the different vascular regions, being highest in the skeletal muscle vasculature and lowest in the splanchnic vascular bed. Moreover, in the skeletal muscle vascular bed, the PGI_2 synthetic pathway is quantitatively the most important.[17]

The falling vascular resistance caused a drop in arterial blood pressure, reaching the level of significance at a dose 10 ng/kg per min. The acceleration of heart rate, which followed, could be looked upon as an autoregulatory mechanism, triggered by a fall in blood pressure. This acceleration together with a slight fall in stroke volume index resulted in the small increase in cardiac index, which did not reach the level of statistical significance. Left ventricular stroke work index decreased significantly during infusion of 10 ng/kg per min PGI_2. Lower doses of PGI_2 (2 and 5 ng/kg per min), which did not reduce afterload, however, caused no changes in either left ventricular stroke work index or cardiac index, left ventricular $\Delta p/\Delta t$, and systolic time interval. It appears, therefore, that PGI_2 in the above doses has no direct inotropic effects.

Our overall impression is that prostacyclin acts predominantly on the resistance vessels. This suggestion stems from the following haemodynamic changes occurring during PGI_2 infusion: (1) fall in vascular resistance; (2) increase in muscle blood flow; (3) lack of changes in mean right atrial pressure. Prostacyclin, therefore, could be valuable not only in the treatment of peripheral arterial disease,[6 18] but also in clinical conditions associated with significant rise in vascular resistance, including pulmonary hypertension, hypertensive emergencies, and cardiogenic shock. Clinical studies with prostacyclin seem warranted in heart failure, a condition affected favourably by vasodilators through lowering of afterload and subsequent improvement of failing left ventricle.[19 20] If prostacyclin, indeed, finds application in the above clinical situations, then it might be advantageous in comparison with the currently used vasodilators, since its potentially useful haemodynamic effects occur even at low doses (2 to 10 ng/kg per min) which cause no serious side effects.

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References

1 Gryglewski RJ, Bunting S, Moncada S, Flower RJ, Vane JR. Arterial walls are protected against deposition of platelet thrombi by a substance (prostaglandin X) which they make from prostaglandin endoperoxides. *Prostaglandins* 1976; **12:** 685–713.

2 Moncada S, Gryglewski RJ, Bunting S, Vane JR. A lipid peroxide inhibits the enzyme in blood vessel microsomes that generates from prostaglandin endoperoxides the substance (prostaglandin X) which prevents platelet aggregation. *Prostaglandins* 1976; **12:** 715–37.

3 Gryglewski RJ, Korbut R, Ocetkiewicz A. Generation of prostacyclin by lungs in vivo and its release into the arterial circulation. *Nature* 1978; **273:** 765–7.

4 Szczeklik A, Gryglewski RJ. The actions of prostacyclin in man. In: Vane JR, Bergström S, eds. *Prostacyclin*. New York: Raven Press, 1979: 393–408.

5 Gryglewski RJ, Szczeklik A. Inhibition of prostacyclin formation by lipid peroxides in the arterial wall: hypothetical step in development of atherosclerosis. *Mater Med Pol* 1978; **37:** 338–41.

6 Szczeklik A, Nizankowski R, Skawiński S, Szczeklik J, Gluszko P, Gryglewski RJ. Successful therapy of advanced arteriosclerosis obliterans with prostacyclin. *Lancet* 1979; **i:** 1111–4.

7 Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation* 1968; **37:** 149–59.

8 Parmley WW, Diamond G, Tomoda H, Forrester JS, Swan HJC. Clinical evaluation of left ventricular pressures in myocardial infarction. *Circulation* 1972; **45:** 358–66.

9 Szczeklik A, Gryglewski RJ, Nizankowski R, Musial J, Pietoń R, Mruk J. Circulatory and antiplatelet effects of intravenous prostacyclin in healthy men. *Pharmacol Res Commun* 1978; **10:** 545–56.

10 Leffler CW, Hessler JR. Pulmonary and systemic vascular effects of exogenous prostaglandin I_2 in fetal lambs. *Eur J Pharmacol* 1979; **54:** 37–42.

11 Spannhake EW, Chapnick BM, Feigen LP, *et al.* Pulmonary and systemic vasodilator effects of prostacyclin (abstract). *Fed Proc* 1978; **37:** 731–5.

12 Armstrong JM, Lattimer N, Moncada S, Vane JR.

Comparison of vasodepressor effects of prostacyclin and 6-oxo-prostaglandin $F_{1\alpha}$ with those of prostaglandin E_2 in rats and rabbits. *Br J Pharmacol* 1978; **62:** 125–30.

13 Fitzpatrick TM, Alter I, Corey EJ, Ramwell PW, Rose JC, Kot PA. Cardiovascular responses to PGI_2 (prostacyclin) in the dog. *Circ Res* 1978; **42:** 192–7.

14 Szczeklik J, Dubiel JS, Mysik M, Pyzik Z, Król R, Horzela T. Effects of prostaglandin E_1 on pulmonary circulation in patients with pulmonary hypertension. *Br Heart J* 1978; **40:** 1397–401.

15 Olsson AG, Carlson LA. Clinical, hemodynamic and metabolic effects of intraarterial infusions of prostaglandin E_1 in patients with peripheral vascular disease. In: Samuelsson B, Paoletti R, eds. *Advances in prostaglandin and thromboxane research.* Vol 1. New York: Raven Press, 1976: 429–31.

16 Kadowitz PJ, Chapnick, BM, Feigen LP, *et al.* Pulmonary and systemic vasodilator effects of the newly discovered prostaglandin, PGI_2. *J Appl Physiol* 1978; **45:** 408–13.

17 Nowak J. Prostaglandins in the cardiovascular system in man. A biochemical and physiological study. *Acta Physiol Scand* 1979; suppl 467: 1–49.

18 Szczeklik A, Gryglewski RJ, Nizankowski R, Skawiński S, Gluszko P. Prostacyclin therapy in peripheral arterial disease. *Thromb Res* (in press).

19 Kelman GR. *Applied cardiovascular physiology.* 2nd ed. London: Butterworths, 1977.

20 Massie BM, Chatterjee K. Vasodilator therapy of pump failure complicating acute myocardial infarction. *Med Clin North Am* 1979; **63:** 25–51.

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Prescribing Information: Presentation Round, biconvex, scored, white tablets containing 2.5mg, 5mg or 10mg minoxidil. Tablets marked 2.5, 5 or 10 on plain side and U on each side of score mark on other side. **Uses** Treatment of severe hypertension. Acts as a peripheral vasodilator and should be used with a diuretic and a beta-blocker. **Dosage and Administration** *Adults* Initial dose 5mg daily as single or divided dosage. Dosage adjustments should be made at intervals of not less than 3 days, until optimal control of blood pressure is achieved. It is seldom necessary to exceed 50mg per day. Dosage may first be increased to 10mg daily and subsequent increases should be by increments of 10mg in the daily dose. *Children* For patients of 12 years of age or below, dose at 0.2mg/kg with increments of 0.1mg-0.2mg/kg in daily dose at minimum of 3-day intervals. Maximum recommended dose is 1.0mg/kg daily. **Rapid reduction of blood pressure** Rapid reduction of blood pressure can be achieved using continuous blood pressure monitoring and incremental doses of 5mg every 6 hours. Loniten therapy should always be accompanied by diuretic and beta-blocker treatment (See Data Sheet). **Contra-indications, warnings etc** *Contra-indications* Phaeochromocytoma. *Warnings* If used alone, Loniten can cause a significant retention of salt and water leading to positive physical signs such as oedema, and to clinical deterioration of some patients with heart failure. Diuretic treatment alone, or in combination with restricted salt intake is, therefore, necessary for all patients taking Loniten. Patients who have had a myocardial infarction should only be treated with Loniten after a stable post-infarction state has been established. The physican should bear in mind that if not controlled by sympathetic suppressants, the rise in cardiac rate and output that follows the use of potent vasodilators may induce anginal symptoms in patients with undiagnosed coronary artery disease, or may aggravate pre-existing angina pectoris. The effect of Loniten may be additive to concurrent antihypertensive agents. The interaction of Loniten with sympathetic blocking agents such as guanethidine or bethanidine may produce excessive blood pressure reduction and/or orthostasis. *Precautions* The safety of Loniten in pregnancy remains to be established. Hypertrichosis occurs in most patients treated with Loniten and all patients should be warned of this possibility before starting therapy. Spontaneous reversal to the pre-treatment state can be expected 1-3 months after cessation of therapy. Soon after starting Loniten therapy approximately 60 per cent of patients exhibit E.C.G. alterations in the direction and magnitude of their T waves. Large changes may encroach on the ST Segment, unaccompanied by evidence of ischaemia. These asymptomatic changes usually disappear with continuing Loniten treatment. The E.C.G. reverts to the pre-treatment state if Loniten is discontinued. Pericardial effusion has been detected in patients treated with a Loniten-containing regime. A cause and effect relationship has not been established. Most effusions have either been present before Loniten was given, or occurred among uraemic patients. However, it is suggested that Loniten-treated patients should be periodically monitored for signs or symptoms of pericardial effusion and appropriate therapy instituted if necessary. Salt and water retention in excess of 2 to 3 pounds may diminish the effectiveness of Loniten. Patients should, therefore, be carefully instructed about compliance with diuretic therapy and a detailed record of body weight should be maintained. *Side-Effects* Most patients receiving Loniten experience a diminution of pre-existing side effects attributable to their disease or previous therapy. New events or side effects likely to increase include peripheral oedema, associated with or independent of weight gain; increases in heart rate; hypertrichosis; and a temporary rise in creatinine and blood urea nitrogen. Gastrointestinal intolerance, rash and breast tenderness are infrequently reported side effects of Loniten therapy. **Pharmaceutical Precautions** None. **Legal Category** POM. **Package Quantities** 2.5mg, 5mg and 10mg Loniten tablets supplied as bottles of 100. **Basic NHS Cost (UK)** 2.5mg – £4.50. 5mg – £8.00. 10mg – £15.50. Data Sheet available on request.

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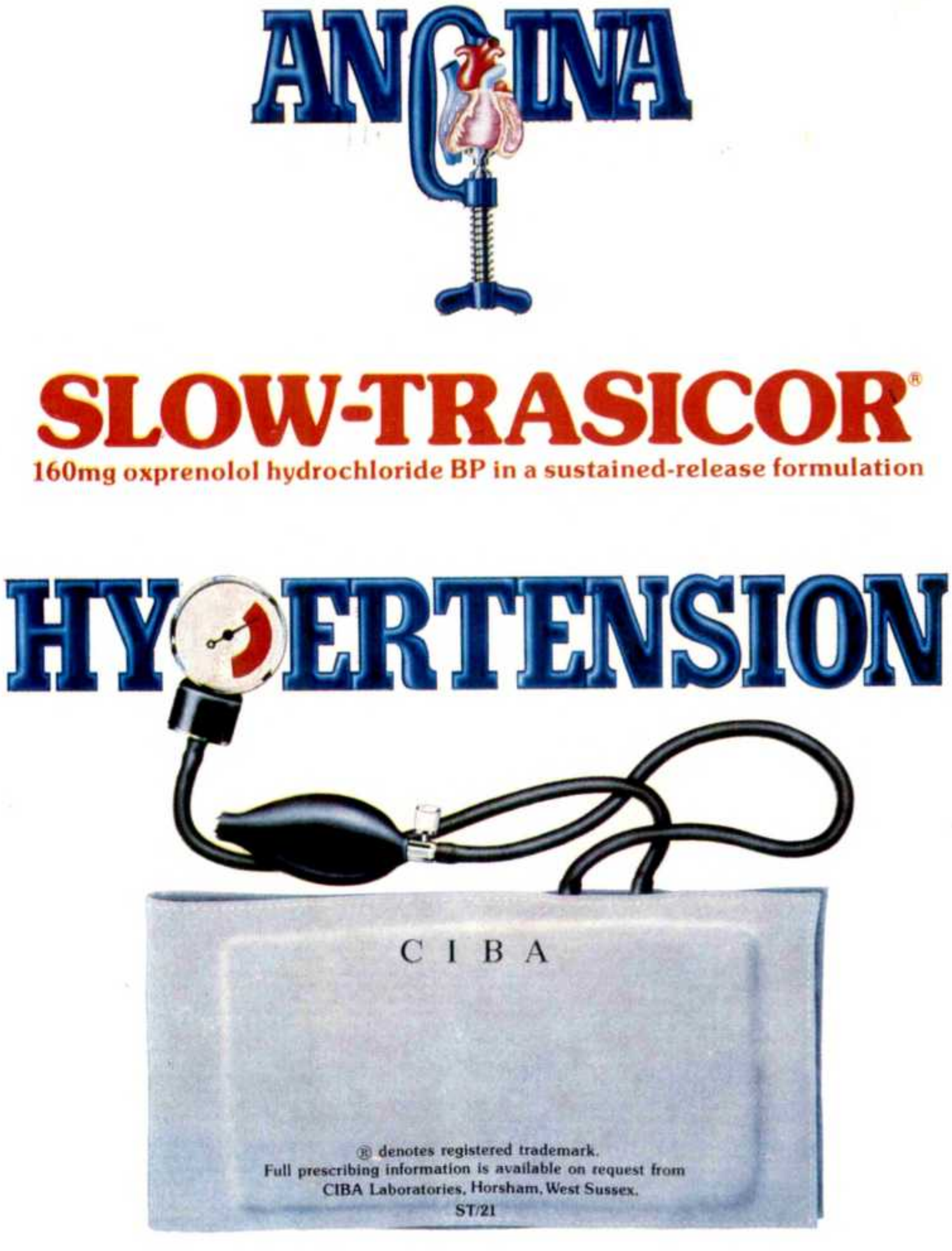

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Br Heart J 1980; **44**: 259–64

Haemodynamic effects of hydralazine at rest and during exercise in patients with chronic heart failure

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SUMMARY The administration of vasodilator drugs has been shown to have beneficial effects at rest in patients with acute or chronic heart failure. To determine the efficacy of hydralazine during exercise, 10 severely symptomatic patients with chronic left ventricular failure from diffuse coronary disease or cardiomyopathy were studied at rest and during upright exercise on a bicycle ergometer. All patients were already receiving optimal treatment with digitalis and diuretics.

At rest treatment with hydralazine resulted in a fall in both mean arterial and pulmonary wedge pressure. There was a 50 per cent reduction in systemic vascular resistance compared with pretreatment measurements and there was an equally impressive increase in stroke volume index. During exertion the changes noted at rest were sustained though occurred to a lesser degree; thus there was a 20 per cent fall in arterial resistance and a 20 per cent rise in stroke volume index compared with control.

These findings show that hydralazine administration not only results in a beneficial effect on cardiac function at rest but that this effect is maintained during upright exercise in patients with impaired left ventricular function, thus providing further support for its use in the long-term management of such patients.

The improvement in survival of patients admitted to coronary care units with acute myocardial infarction and the reduction in post-infarct mortality with the use of antiarrhythmic treatment has resulted in an increasing number of patients who manifest symptoms and signs of poor ventricular function and in whom the use of conventional antifailure treatment with digitalis and diuretics has failed to result in significant improvement. In these patients and in patients with ventricular failure resulting from other forms of cardiomyopathy, the administration of vasodilator drugs has been shown to result in beneficial haemodynamic changes.[1–6]

Thus sodium nitroprusside given intravenously lowers systemic vascular resistance and reduces impedance to ventricular ejection. Consequently cardiac output increases with only small changes in the arterial pressure. At the same time, because of more effective ventricular emptying and because of an increase in venous capacitance consequent upon the venodilatory effects of nitroprusside, ventricular filling pressures are reduced. Thus the two major effects of chronic pump failure are alleviated—namely impaired organ perfusion and raised pulmonary venous pressure. While these beneficial effects follow the acute administration of intravenous sodium nitroprusside, its use in the long-term management of heart failure is clearly not feasible. Further studies have therefore examined the effects of other vasodilator drugs which can be administered orally. Nitrates qualitatively mimic the effects of treatment with nitroprusside by causing a significant reduction in left ventricular filling pressure[7 8] but a less impressive change in cardiac output.[9 10]

Treatment with hydralazine, an arterial dilator, increases the cardiac output as much as nitroprusside but seems to be less effective in reducing left ventricular filling pressure.[11–16]

These studies have analysed the acute effects of drugs used at rest and little attention has been paid to their effects during upright exercise where the major benefit of such treatment would be sought. The present study has therefore been undertaken to assess the haemodynamic effects of orally admininistered hydralazine, at rest and during upright bicycle exercise, in patients with chronic left ventricular failure from myocardial disease.

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Table 1 *Haemodynamic effects of hydralazine at rest*

		Before drug							*After drug*	
Case no.	*Aet*	*HR (b/min)*	*MPAP (mmHg)*	*PCWP (mmHg)*	*MAP (mmHg)*	*CI (l/min per m^2)*	*SVR units*	*SVI (ml/m^2)*	*HR (b/min)*	*MPAP (mmHg)*
1	CD	100	47	28	100	1·50	40	15	98	55
2	CD	89	35	27	80	1·252	29	17	85	35
3	CD	105	16	5	84	1·49	31	14	107	12
4	CD	100	25	16	80	2·053	24	20	100	25
5	CD	90	29	22	80	2·053	24	23	100	32
6	CD	90	13	8	92	2·455	24	27	85	13
7	CM	70	26	18	90	1·60	27	23	70	20
8	CM	135	18	5	88	1·98	26	15	162	17
9	AVR	63	57	32	92	1·672	31	27	68	54
10	CM	90	25	17	84	2·535	18	28	90	22
Group data (SEM ±)		93 ±6	29 ±4	18 ±3	87 ±2	1·886 ±0·12	27 ±2	21 ±2	97 ±8	29 ±5

HR, heart rate; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; MAP, mean arterial pressure; SVR, systemic vascular resistance; SVI, stroke volume index; CD, coronary artery disease; CM, dilated cardiomyopathy; AVR, aortic valve replacement.

Patients and methods

Ten patients with chronic heart failure were studied. There were seven men and three women, with an age range of 44 to 72 years (mean 61 years). The aetiology of the ventricular failure was secondary to diffuse coronary arterial disease in six patients, caused by cardiomyopathy of unknown cause in three patients, and was related to persistent poor ventricular function despite aortic valve replacement for severe aortic regurgitation in one patient. Clinically, all patients had symptoms and signs of chronic severe biventricular failure and the chest *x*-ray showed typical cardiomegaly and evidence of pulmonary venous hypertension. All patients were being optimally treated with conventional treatment including digoxin and diuretics.

Before the definitive haemodynamic evaluation, each patient participated in at least two exercise practice sessions in order to become familiar with the bicycle ergometer procedure and in order to assess maximum exercise capacity. Exercise was performed at an initial workload of 20 watts and was increased by 20 watts every three minutes. Exercise continued until the patient felt unable to proceed because of severe dyspnoea or fatigue. Exercise tolerance on the ergometer during the preliminary studies was found to be reproducible in all patients.

During the definitive haemodynamic studies, arterial pressure was measured by means of a short Teflon catheter inserted percutaneously into the brachial artery. Pulmonary capillary wedge pressure was obtained by inserting a balloon-tipped triple lumen catheter through a basilic vein. Cardiac output was determined in triplicate using thermodilution techniques. For convenience, pressure measurements were made with zero reference to

Table 2 *Haemodynamic effects of hydralazine during exercise*

		Before drug							*After drug*	
Case no.	*Aet*	*HR (b/min)*	*MPAP (mmHg)*	*PCWP (mmHg)*	*MAP (mmHg)*	*CI (l/min per m^2)*	*SVR units*	*SVI (ml/m^2)*	*HR (b/min)*	*MPAP (mmHg)*
1	CD	140	55	33	105	3·497	18	25	135	50
2	CD	115	35	25	70	2·202	18	19	115	—
3	CD	140	34	24	75	2·14	19	15	140	27
4	CD	120	52	35	80	4·061	12	34	115	40
5	CD	125	50	32	85	4·28	12	34	130	50
6	CD	135	25	21	84	5·486	10	41	135	24
7	CM	90	45	30	90	3·60	13	40	85	33
8	CM	220	42	26	118	5·40	13	25	195	30
9	AVR	87	56	35	65	2·287	16	26	80	55
10	CM	130	57	35	85	4·672	10	36	120	45
Group data (SEM ±)		130 ±12	46 ±4	30 ±2	86 ±5	3·763 ±0·4	14 ±1	29 ±3	125 ±10	39 ±4

For abbreviations, see Table 1.

PCWP *(mmHg)*	*MAP* *(mmHg)*	*CI* *(l/min per m²)*	*SVR* *units*	*SVI* *(ml/m²)*
30	94	1·887	30	19
22	74	2·279	18	27
2	62	2·314	15	22
15	70	3·794	11	38
20	80	3·159	16	32
3	54	3·454	10	41
5	65	3·10	11	44
4	60	3·60	10	22
30	69	2·663	15	39
10	78	3·937	11	44
14 ±3	71 ±4	3·019 ±0·22	15 ±2	33 ±3

the sternal angle. Baseline haemodynamic measurements were obtained with the patient sitting upright at rest on the bicycle ergometer. The patient then performed graded exercise to the point of maximal exercise tolerance when haemodynamic recordings were repeated before the termination of exercise with dyspnoea or fatigue. After this control study the patients rested supine and were given 50 to 75 mg hydralazine orally (a dose of 1 mg/kg body weight was given based on earlier haemodynamic observations). Cardiac output determinations and pressure measurements were repeated at rest and during maximum exertion three hours later.

Results

Tables 1 and 2 show the haemodynamic variables in the 10 patients both at rest and during maximal exercise, before and three hours after the oral administration of hydralazine.

Under resting conditions hydralazine produced a significant fall in mean pulmonary venous pressure from an average of 18 ±3·0 to 14 ±3·5 mmHg ($p < 0·05$); at peak exercise, a significant reduction in mean wedge pressure also occurred after treatment, from 30 ±1·6 to 23 ±1·1 mmHg ($p < 0·01$) (Fig. 1). Similar haemodynamic effects on mean arterial pressure were observed. Thus mean arterial pressure fell from 87 ±2·1 to 70 ±3·6 mmHg ($p < 0·01$) after treatment at rest and from 86 ±5·0 to 76 ±3·9 mmHg ($p < 0·01$) during peak exercise (Fig. 2). The fall in arterial pressure was related to a striking reduction in arterial resistance. At rest, arterial resistance fell from an average of 27 ±1·9 units, for the group as a whole, to 15 ±1·9 units ($p < 0·01$) after treatment with hydralazine. As can be seen (Fig. 3) this was similar to the average level of resistance measured in the patients during exercise before hydralazine had been given. During exercise three hours after the drug, there was then a further significant reduction in resistance to 11 ±0·8 units ($p < 0·01$). Coincident with the alteration in systemic vascular resistance, there was an impressive increase in stroke volume both at rest and during maximal exertion (Fig. 4). At rest, stroke volume increased significantly from an average of 21 ±1·7 to 33 ±3·1 ml/m² after hydralazine ($p < 0·01$) and indeed returned to the normal range (> 35 ml/m²) in several instances. During effort stroke volume increased from a mean of

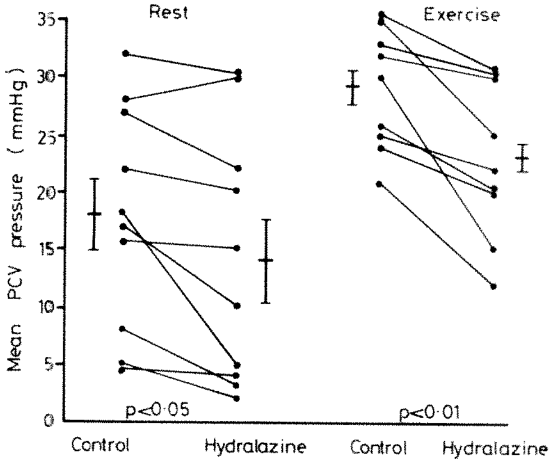

Fig. 1 *The haemodynamic effects of hydralazine on mean pulmonary capillary venous pressure (SEM shown) both at rest* (left-hand panel) *and during upright exercise* (right-hand panel).

PCWP *(mmHg)*	*MAP* *(mmHg)*	*CI* *(l/min per m²)*	*SVR* *units*	*SVI* *(ml/m²)*
30	94	3·845	15	29
20	60	2·345	14	21
22	67	2·656	14	19
25	70	4·897	9	43
30	86	4·669	12	36
12	70	5·075	9	38
15	84	4·40	9	53
20	88	6·1	8	31
30	60	3·087	11	39
30	80	5·768	8	48
23 ±2	76 ±4	4·285 ±0·4	11 ±1	36 ±3

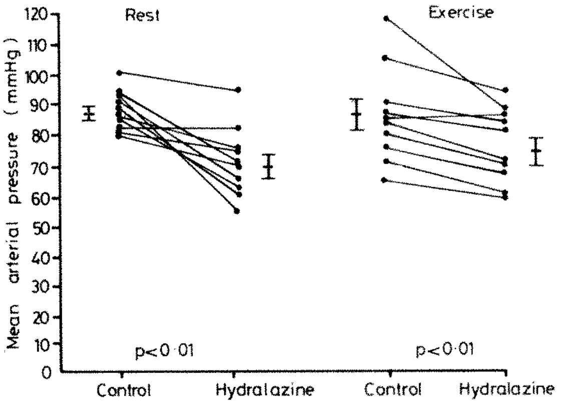

Fig. 2 *The haemodynamic effects of hydralazine on mean arterial pressure (SEM shown) both at rest* (left-hand panel) *and during upright exercise* (right-hand panel).

29 ±2·8 to 36 ±3·4 ml/m² after treatment ($p < 0·01$). In one patient stroke volume actually fell during exertion after hydralazine (41 to 38 ml/m²) and this was probably related to an excessive reduction in filling pressure induced by the drug in this patient.

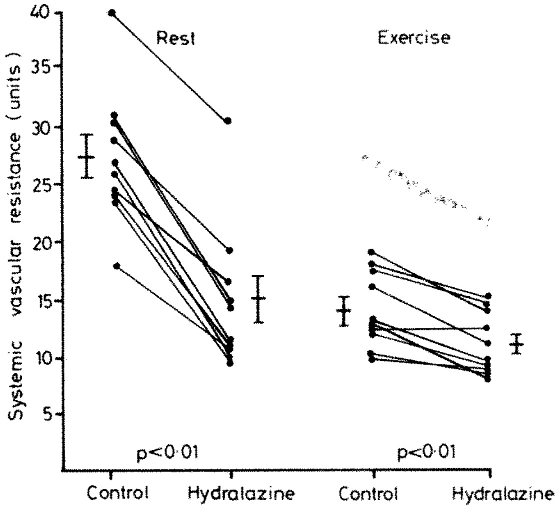

Fig. 3 *The haemodynamic effects of hydralazine on systemic vascular resistance (SEM shown) both at rest* (left-hand panel) *and during upright exercise* (right-hand panel).

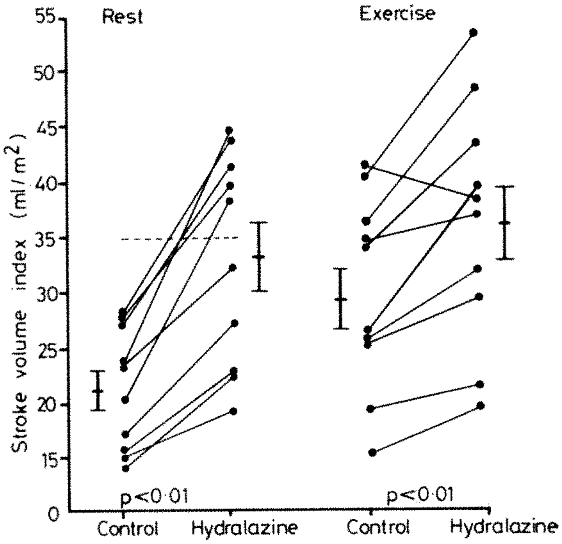

Fig. 4 *The haemodynamic effects of hydralazine on stroke volume index (SEM shown) both at rest* (left-hand panel) *and during upright exercise* (right-hand panel).

The haemodynamic changes occurring after treatment with hydralazine may be expressed as the average percentage change compared with pre-treatment measurements. At rest, there was a significant reduction in both arterial and pulmonary wedge pressure. There was a 50 per cent reduction in systemic vascular resistance and an equally striking increase in stroke volume index. During exertion the shifts seen in the resting state were maintained but occurred to a considerably lesser degree; thus there was a 20 per cent fall in systemic vascular resistance and a 20 per cent rise in stroke volume index compared with control. In order to analyse the effects of hydralazine on left ventricular performance, points on the function curve were plotted in the conventional manner by comparing the average pulmonary wedge pressure with the average stroke volume index, both at rest and at peak exercise (Fig. 5). At rest, stroke volume index increased from 21 to 33 ml/m² after hydralazine while there was a coincident slight but significant reduction in filling pressure (from 18 to 14 mmHg). During exercise treatment with hydralazine resulted in a similar directional change in stroke volume (from 29 to 36 ml/m², $p < 0·01$). Thus there appeared to be an overall shift of the function curve upwards and to the left suggesting improved left ventricular function.

Discussion

Systemic vascular resistance is increased in the setting of chronic left ventricular failure since arterial pressure is often normal or sometimes raised in the face of a pronounced reduction in cardiac output.[17] Multiple factors may be respon-

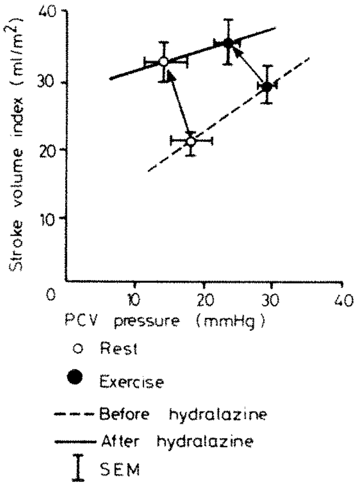

Fig. 5 *The effect of hydralazine on left ventricular performance both at rest* (left-hand side) *and during maximal exertion* (right-hand side).

sible for this high vascular resistance. Increased sympathetic outflow, enhanced secretion of renin, and the accumulation of salt and water in the blood vessels may each be determinants in the process.[18 19]

An increase in systemic vascular resistance in response to a decrease in cardiac output is appropriate and beneficial when a fall in cardiac output is not associated with primary pump dysfunction but, in contrast, when left ventricular function is impaired, the increase in impedance further diminishes cardiac output and consequently further compromises the already decreased function. Vasodilator therapy therefore represents a means of interrupting an undesirable positive feedback mechanism that may play an important part in the natural history of heart failure. The overall improvement in cardiac function with hydralazine is most probably the result of a direct dilating effect on resistance vessels previously noted by others.[11–14] The decrease in impedance to left ventricular ejection shown in this study is therefore presumably responsible for the increase in cardiac output and is similar to the observations, measured under resting conditions, reported by Chatterjee *et al.*[15] and Franciosa *et al.*[16] In this study, treatment with hydralazine alone produced a small but significant reduction in arterial and pulmonary wedge pressure which differs from the results of Chatterjee *et al.*[15] and may be related to the larger dose of hydralazine used, to the different composition of two relatively small groups, and to the variation of metabolism of hydralazine in different patients. The blood levels of the active metabolites of hydralazine are dependent on the individual rate of hepatic acetylation when the drug is given orally; the blood level of hydralazine is approximately 50 per cent of the oral dose in slow acetylators but only 30 per cent in fast acetylators.

The reduction in left ventricular filling pressure after treatment with hydralazine is a probable consequence of more effective left ventricular emptying resulting from decreased impedance to ejection. This reduction in diastolic pressure and volume will result in an improved oxygen demand: supply ratio which will prevent or delay myocardial ischaemia during stress in patients with ischaemic cardiomyopathy and thus help to preserve myocardial function.

During peak exercise the magnitude of change in cardiac output after treatment with hydralazine is less obvious for the group overall than that observed under resting conditions. This is an expected finding, since it would be very unlikely, that under conditions of stress, impaired pump function would be able to improve as much as at rest however potent the stimulus. In addition, quite distinct variations between patients in the increment in cardiac output during exercise after hydralazine were observed and this probably related to the aetiology of the heart failure, its severity, and duration. Exercise tolerance in all patients, when assessed after the acute administration of hydralazine, was not improved even in those subjects where a considerable increase in cardiac output had been measured during maximal exertion. It is possible, therefore, that hydralazine results in an increase in cardiac output which is preferentially distributed to cutaneous, hepatic, splanchnic, and renal vascular compartments.[11 20]

In conclusion this study confirms the beneficial effect of hydralazine on resting cardiac function in patients with chronic heart failure. This improvement in cardiac function is sustained, though to a lesser extent, during upright exercise. Though these results provide further support for the use of vasodilators in the long-term management of patients with chronic heart failure, questions arise concerning the wide individual patient variation in response to treatment. Furthermore, though cardiac output is increased by hydralazine, more information about the regional vascular effects of such agents is required.

References

1 Franciosa JA, Guiha NH, Limas CJ, Rodriguera E, Cohn JN. Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. *Lancet* 1972; **i:** 650–4.

2 Chatterjee K, Parmley WW, Ganz W, *et al.* Hemodynamic and metabolic response to vasodilator therapy in acute myocardial infarction. *Circulation* 1973; **48:** 1183–93.

3 Chatterjee K, Parmley WW, Swan HJC, Berman G, Forrester J, Marcus HS. Beneficial effect of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvar apparatus. *Circulation* 1973; **48:** 684–90.

4 Guiha MH, Cohn JM, Mikulic E, Franciosa JA, Limas JC. Treatment of refractory heart failure with infusion of nitroprusside. *N Engl J Med* 1974; **291:** 587–92.

5 Miller RR, Vismara LA, Zelis R, Amsterdam EA, Mason DT. Clinical use of sodium nitroprusside in chronic ischemic heart disease. *Circulation* 1975; **51:** 328–36.

6 Bolen JL, Alderman EL. Hemodynamic consesequences of afterload reduction in patients with chronic aortic regurgitation. *Circulation* 1976; **53:** 879–83.

7 Mason DT, Braunwald E. The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. *Circulation* 1965; **32:** 755–66.

8 Miller RR, Vismara LA, Williams DO, Amsterdam GA, Mason DT. Pharmacological mechanisms for left ventricular unloading in clinical congestive heart failure. *Circ Res* 1976; **39:** 127–33.

9 Armstrong PW, Walker DC, Burton JR, Parker JO. Vasodilatory therapy in acute myocardial infarction. *Circulation* 1975; **52:** 1118–22.

10 Williams DO, Amsterdam EA, Mason DT. Hemodynamic effects of nitroglycerine in acute myocardial infarction. *Circulation* 1975; **51:** 421–7.

11 Freis ED, Rose JC, Higgins TF, Finnerty FA Jr, Kelley RT, Partenope EA. The hemodynamic effects of hypotensive drugs in man; 4 : 1-hydrazinophthalazine. *Circulation* 1953; **8:** 199–204.

12 Stunkard A, Wertheimer L, Redisch W. Studies on hydralazine; evidence for a peripheral site of action. *J Clin Invest* 1954; **33:** 1047–53.

13 Rowe GG, Huston JH, Maxwell GM, Crossley AP Jr, Crumpton CW. Hemodynamic effects of 1-hydrazinophthalazine in patients with arterial hypertension. *J Clin Invest* 1955; **34:** 115–20.

14 Ablad B. A study of the mechanism of the hemodynamic effects of hydralazine in man. *Acta Pharmacol Toxicol* 1963; **20,** suppl I: 53.

15 Chatterjee K, Parmley WW, Massie B, *et al.* Oral hydrallazine therapy for chronic refractory heart failure. *Circulation* 1976; **54:** 879–83.

16 Franciosa JA, Pierpont G, Cohn JM. Hemodynamic improvement after oral hydrallazine in left heart failure. *Ann Intern Med* 1977; **86:** 388–93.

17 Stead EA Jr. The role of the cardiac output in the mechanisms of congestive heart failure. *Am J Med* 1949; **6:** 232–6.

18 Chidsey CA, Harrison DC, Braunwald E. Augmentation of the plasma nor-epinephrine response to exercise in patients with congestive heart failure. *N Engl J Med* 1962; **267:** 650–4.

19 Zelis R, Mason DT, Braunwald E. A comparison of the effects of vasodilator stimuli on peripheral resistance vessels in normal subjects and in patients with congestive heart failure. *J Clin Invest* 1968; **47:** 960–70.

20 Johnston BM. The use of radioactive microspheres to compare the effects of hydralazine, guanethidine and SK and F 24260 on the redistribution of cardiac output in anaesthetized rabbits. *Br J Pharmacol* 1975; **55:** 393–402.

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Cardiovascular reflexes in patients after myocardial infarction

Effect of long-term treatment with beta-adrenoceptor antagonists

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SUMMARY A double-blind study was made of men who had had a myocardial infarction at least one year previously, and who were being treated with propranolol, atenolol, or placebo. They were compared with age- and sex-matched control subjects. Under resting conditions, there were no differences between the systemic arterial blood pressures, forearm blood flows, or heart rates of the control subjects and the post-infarction patients treated with placebo. The patients, however, showed signs of reduced sympathetic effects on the cardiovascular system when their reflex responses to the Valsalva manoeuvre, lower body negative pressure, and performance of a mental task were assessed. Long-term treatment with propranolol or atenolol had little effect on resting systemic arterial blood pressure or forearm blood flow, but caused a significant reduction in resting heart rate. Differences in the reflex responses of these patients and those on placebo were attributable to the effects of the beta-adrenoceptor antagonists on resting heart rate. These results indicate that post-infarction patients do not have signs of overactivity of autonomic nervous control of the cardiovascular system. Furthermore, long-term treatment of such patients with beta-adrenoceptor antagonists does not impair cardiovascular reflexes.

Patients with an acute myocardial infarction frequently have physical signs suggestive of excessive autonomic nervous system activity. A sinus tachycardia and systemic hypertension may indicate overactivity of the sympathetic nervous system, while sinus bradycardia may indicate overactivity of the parasympathetic system.[1] It has been suggested that such autonomic "imbalance" may contribute to the high mortality of acute infarction.[1] On the other hand, it is possible that activation of the sympathetic system is a desirable reflex response that tends to improve cardiac performance, while parasympathetic-mediated bradycardia may have the useful function of reducing myocardial oxygen demand.

Reflexes mediated through the autonomic system are difficult to investigate when patients are ill, but within the first few days after infarction it has been shown that the bradycardia induced by face immersion (the "diving reflex") is increased, possibly indicating sensitisation of cardiac parasympathetic control.[2] This change is temporary,[3] and little is known about other cardiovascular reflex mechanisms in patients who have suffered a myocardial infarction.[3 4]

The value of long-term treatment with beta-adrenoceptor antagonists after a myocardial infarction is still not clear. Though they have been claimed to reduce mortality, the mechanism by which they do so is unknown. They do not appear to have much antiarrhythmic effect[5] but one possibility is that they modify cardiovascular reflexes in a way that protects the heart from undesirable autonomic nervous influence.

We have therefore compared cardiovascular reflexes in a group of survivors of myocardial infarction (who were either untreated, or who had received beta-adrenoceptor antagonists for at least one year) with those of a matched group of healthy subjects.

Subjects and methods

Twenty-four men aged less than 60 years, who had

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had a proven myocardial infarction at least 12 months previously, were studied. None suffered from angina or had symptoms or signs of heart failure; all had returned to their preinfarction level of activity. All were taking part in a trial comparing propranolol (a non-selective beta-adrenoceptor antagonist[6]), atenolol (a cardioselective beta-adrenoceptor antagonist[6]), or placebo in post-infarction patients. In that trial, the results of which will be described elsewhere (Wilcox *et al.*, in preparation), treatment began immediately after admission to a coronary care unit; thus the patients described in the present study had received either a beta-adrenoceptor antagonist or placebo for at least 12 months. No patient was receiving any other treatment.

Table 1 *Details of control subjects and post-infarction patients*

Group	*No.*	*Age (y)*	*Months since infarct*	*Maximum enzyme levels*	
				SHBD	*AST*
Control	6	47 ±2	—	—	—
Placebo	6	52 ±3	17 ±1	576	108
Propranolol	6	42 ±4	15 ±1	584	115
Atenolol	6	48 ±3	15 ±1	598	101

The amounts of beta-adrenoceptor antagonists administered (propranolol 80 mg bd and atenolol 50 mg bd) were thought to be equipotent in terms of heart rate and blood pressure reduction,[6] and were considered to be the maximum doses likely to be acceptable to the patients.

The ratios of anterior to inferior infarctions in the three treatment groups were: propranolol 5:1; atenolol 4:2; placebo 4:2.

The volunteer men who acted as age-matched controls were all members of the ambulance service. None had any known cardiovascular or other illness and none was taking any drug.

All the subjects gave their written consent to the investigation which was approved by the medical school ethical committee.

Assessment of cardiovascular reflexes was carried out in a temperature-controlled room set at 24°C, between 2.0 and 4.0 pm after a light lunch. All subjects rested quietly for 30 minutes before testing started and during that time chest leads were attached from which an electrocardiogram could be recorded and heart rate derived by feeding the signal into an instantaneous ratemeter (Devices Ltd.). Blood pressure was measured by sphygmomanometry in the left arm and forearm blood flow was measured in the right arm by venous occlusion plethysmography, using a mercury-in-silastic strain gauge.[7] Forearm vascular resistance was derived by dividing mean blood pressure (diastolic pressure + one-third pulse pressure) by forearm blood flow.

Blood pressure and forearm blood flow were measured every 15 seconds during the baseline periods, which lasted at least three minutes. The coefficients of variation for blood pressure and flow during the last minute before any particular manoeuvre being carried out were invariably less than 5 per cent in any individual.

Cardiovascular reflexes were assessed using the following manoeuvres.

(1) HEART RATE VARIABILITY DURING DEEP BREATHING

Variation in RR interval during respiration (sinus arrhythmia) is dependent upon vagal efferent integrity, and is a reliable means of assessing it.[8] The depth of respiration is not critical as long as the tidal volume is in excess of 40 per cent of the forced vital capacity, but the rate of breathing is important and was standardised at about six per minute.[8] Heart rate variability was measured as the mean difference between maximal and minimal heart rate during this manoeuvre, with subjects supine.

(2) VALSALVA MANOEUVRE

The subjects performed a Valsalva manoeuvre by blowing into a mouthpiece and holding a column of mercury at a height of 40 mm for 15 seconds. A side-arm air leak prevented them from supporting the column by occluding the mouthpiece. Heart rate was recorded continuously throughout the

Table 2 *Resting cardiovascular status and heart rate variability in groups studied*

	Blood pressure (mmHg)		*Heart rate (beats/min)*	*Variability (beats/min)*
	Systolic	*Diastolic*		
Control subjects	122 ±6·0	79 ±3·0	79 ±7·4	19·2 ±3·2
Placebo group	125 ±6·0	89 ±5·0	74 ±9·2	14·8 ±2·5
Propranolol group	110 ±5·0	74 ±3·0	56 ±1·3*	11·7 ±2·0
Atenolol group	116 ±6·0	78 ±4·0	60 ±4·4*	14·2 ±3·5

* $p < 0·05$ for difference between treated groups and control and placebo treated subjects.

manoeuvre, while blood pressure and forearm blood flow were recorded in the 15 seconds before and within 10 seconds after the manoeuvre.

(3) LOWER BODY NEGATIVE PRESSURE

Enclosure of the body of a supine subject, distal to the level of the iliac crests, in an airtight box permits the application of negative pressure to the enclosed parts; blood pools in the veins exposed to the negative pressure, and the resulting reduction in venous return is similar to that which occurs on moving from the supine to the upright posture.[9] The advantage of the technique is that it provides a means of assessing cardiovascular responses to a reduction in central blood volume without the subject moving and thereby interfering with the measurements. Subjects were exposed to increasing levels of lower body negative pressure ranging from 5 to 40 mmHg below atmospheric pressure for periods of one minute, with recovery periods of at least one minute between each. Heart rate was measured continuously and brachial arterial blood pressure and forearm blood flow were measured at 15 second intervals. In each individual, values obtained in the 15 seconds immediately before negative pressure were compared with those measured during the last 15 seconds of negative pressure.

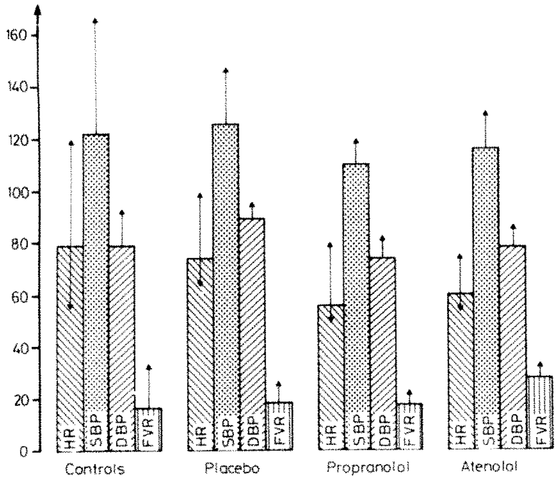


Fig. 1 *Cardiovascular responses to the Valsalva manoeuvre. The blocks represent the resting values of the variables measured (HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; FVR, forearm vascular resistance), the arrows indicate the maximum (for HR, minimum also) values elicited by the manoeuvre. The common axis is for beats/min, mmHg, and arbitrary resistance units.*

Table 3 *Maximum change in cardiovascular variables with lower body negative pressure at 40 mmHg*

	Change in heart rate (beats/min)	*Change in systolic blood pressure (mmHg)*	*Change in forearm vascular resistance (arbitrary units)*
Controls	+18 ±2·5	−10 ±2·5	+33 ±9·5
Placebo group	+6 ±2·0	−24 ±5·0	+10 ±4·4
Propranolol group	+4 ±3·0	−13 ±4·5	+15 ±5·8
Atenolol group	+5 ±2·5	−13 ±4·0	+32 ±9·5

(4) PERFORMANCE OF A MENTAL TASK

Performance of a mental task elicits an increase in heart rate and systemic arterial blood pressure which are sympathetically mediated.[10] In the present test, subjects (sitting) were shown a series of cards on which were written the names of colours in inks of different colours (for example the name green written in red ink etc.). Subjects were asked the name of the colour or the colour of ink (Bennett and Fentem, unpublished observations), and the maximum heart rates and arterial blood pressures were compared during the test which lasted about one minute.

Results quoted in the text are mean values ±SEM; differences between group values were compared by Student's paired or unpaired t tests as appropriate. Slopes of regressions were compared by covariance analysis.

Results

The details of the patients and control subjects are shown in Table 1. Their supine resting blood pressures, heart rates, and heart rate variability during deep breathing are shown in Table 2. The resting heart rates in the patients treated with propranolol or atenolol were significantly lower than those of the controls or placebo-treated patients, but there were no other significant differences.

COMPARISON OF CONTROL SUBJECTS WITH PLACEBO-TREATED POST-INFARCTION PATIENTS

During the Valsalva manoeuvre, the control subjects showed a significantly ($p < 0{\cdot}05$) greater tachycardia than the patients, and after the manoeuvre their overshoot in systolic blood pressure and the accompanying bradycardia were more pronounced ($p < 0{\cdot}05$) (Fig. 1). The bradycardia relative to the pressure overshoot was similar, however, in control subjects and patients. The Valsalva manoeuvre elicited changes in diastolic blood pressure and forearm vascular resistance which were not significantly different in the control subjects and patients (Fig. 1).

On exposure to lower body negative pressure the fall in systolic pressure was less and the increase in forearm vascular resistance was greater in the control subjects, but this difference did not achieve significance, probably because of the large intra-individual variation (Table 3). The post-infarction patients, however, showed a smaller rise in heart rate ($p < 0{\cdot}05$, Table 3), and examination of RR interval and systolic blood pressure during lower body negative pressure showed that there was a significant ($p < 0{\cdot}05$) difference between the slopes for this relation in the control subjects and the patients (Fig. 2).

The pressor response to mental stress was similar in control subjects and placebo-treated, post-infarction patients (Table 4), though the tachycardia was less ($p < 0{\cdot}05$) in the latter group (Table 4).

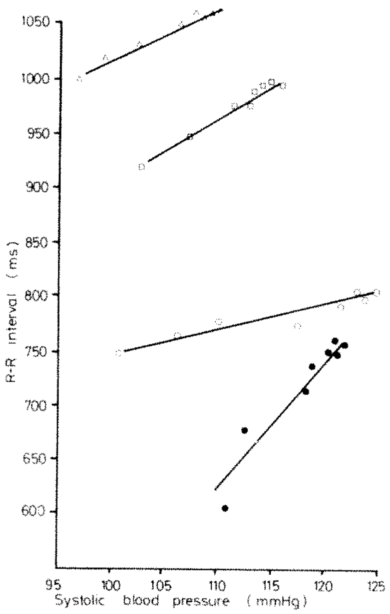


Fig. 2 *Regressions of RR interval on systolic blood pressure during lower body negative pressure (LBNP). For each level of LBNP, RR interval and systolic blood pressure were measured during the last 15 seconds of a one minute exposure. In the control subjects (●) increasing levels of LBNP caused progressive falls in systolic blood pressure and shortening of RR intervals; the slope of the regression (11·5 ms/mmHg) may be taken as an index of baroreflex sensitivity.*[12] *The slope for the placebo-treated patients ○, 2·5 ms/mmHg) is significantly ($p < 0{\cdot}02$) less than that of the control subjects but not different from that of the propranolol-treated (□, 6·0 ms/mmHg) or atenolol-treated (△, 5·0 ms/mmHg) patients.*

Table 4 *Maximum change in systemic arterial blood pressure and heart rate during performance of mental task*

	Change in systolic blood pressure (mmHg)	*Change in diastolic blood pressure (mmHg)*	*Change in heart rate (beats/min)*
Controls	+30 ±1·5	+17 ±2·1	+22 ±2·7
Placebo group	+24 ±2·0	+17 ±1·9	+11 ±1·5
Propranolol group	+17 ±2·5	+16 ±1·5	+14 ±2·0
Atenolol group	+22 ±2·7	+21 ±2·1	+12 ±1·4

COMPARISON OF PLACEBO-TREATED AND BETA-ADRENOCEPTOR ANTAGONIST-TREATED POST-INFARCTION PATIENTS

During the Valsalva manoeuvre the maximum heart rates seen in the propranolol-treated or atenolol-treated patients were significantly ($p < 0{\cdot}05$) lower than in the placebo-treated patients, but this was entirely attributable to the differences in the resting state (Fig. 1), as were the differences in maximum systolic pressures seen after the manoeuvre. While the bradycardia after the manoeuvre was less ($p < 0{\cdot}05$) in the propranolol- or atenolol-treated patients, the bradycardia relative to the pressure overshoot was similar in all groups of patients. The changes in diastolic blood pressure and forearm vascular resistance elicited by the Valsalva manoeuvre were not different in the three groups of patients (Fig. 1).

The patterns of cardiovascular response to lower body negative pressure were similar in all three groups of patients (Table 3), and the slopes for the regressions of RR interval on systolic blood pressure during lower body negative pressure showed no significant differences between the placebo-treated and beta-adrenoceptor antagonist-treated patients (Fig. 2).

The cardiovascular responses to mental stress were similar in all three groups of patients (Table 4).

Discussion

We studied asymptomatic patients who had sustained myocardial infarction more than a year previously. It is possible that patients with heart failure or other complications of the infarction would have shown different responses to our tests of autonomic nervous function.

Under resting conditions the patients treated with placebo had similar heart rates and blood pressures to the healthy subjects. The tests of cardiac parasympathetic effects (heart rate variability[8] and cardiac slowing relative to the pressure overshoot after the Valsalva manoeuvre[11]), showed no differences between these groups. Some tests of cardiovascular sympathetic effects, however, indicated a relative reduction of activity in the post-infarction patients compared with healthy subjects. The patients showed less tachycardia during the Valsalva manoeuvre,[11] during lower body negative pressure,[12] and during performance of a mental task.[13] In the patients there was also a smaller overshoot of blood pressure after the Valsalva manoeuvre, and there was a relatively greater fall in blood pressure and a smaller increase in peripheral vascular resistance in response to lower body negative pressure. All these changes are consistent with reduced sympathetic efferent effects, but as the pressor response to mental stress was intact, some sympathetic efferent pathways must have been normal in these patients. It is possible that the post-infarction patients had some abnormality on the afferent side of the reflex arc, but it is difficult to envisage a single abnormality that would account for the responses seen. It is, of course, by no means certain that the differences in sympathetic responses that we detected between the control subjects and the post-infarction patients were the results of the previous infarction. For example, it is quite possible that they were the result of different levels of habitual activity in the two groups.

Long-term treatment with either a cardio-selective or a nonselective beta-adrenoceptor antagonist had remarkably little effect on the results of our tests of autonomic function. Patients treated with propranolol or atenolol had significantly lower resting heart rates than patients treated with a placebo, a finding consistent with the known effects of these drugs. The reduction in the overshoot of systolic arterial pressure after the Valsalva manoeuvre in these patients could be attributed to the effect of the drugs on cardiac output, as has been seen in subjects treated acutely.[14] Performance of a mental task, however, elicited changes in heart rate and systolic arterial pressure which, as percentages of the resting values, were similar to those seen in the placebo-treated patients. This may indicate that long-term treatment with beta-adrenoceptor antagonists does not attenuate the cardiovascular effects of cortical activation.

Our findings show that several months after a myocardial infarction the parasympathetic innervation of the heart functions normally, though the sympathetic innervation of the cardiovascular system has, for some reason, lesser effects than in normal subjects. There is nothing to suggest that patients who have had an infarction have overactive autonomic nervous systems that might prejudice their response to an infarction. The "autonomic imbalance" seen in acute myocardial infarction is therefore likely to be a result and not a cause of infarction.

It seems that long-term treatment with beta-adrenoceptor antagonists does not have a distinct effect on cardiovascular reflexes in post-infarction patients.

We are grateful to Dawn Lake for technical assistance, and to Professor P H Fentem for his criticism of the manuscript.

References

1 Webb SW, Adgey AAJ, Pantridge JF. Autonomic disturbance at onset of acute myocardial infarction. *Br Med J* 1972; **iii:** 89–92.

2 Gooden BA, Holdstock G, Hampton JR. The magnitude of the bradycardia induced by face immersion in patients convalescing from myocardial infarction. *Cardiovasc Res* 1978; **12:** 239–42.

3 Ryan C, Hollenberg M, Harvey DB, Gwynn R. Impaired parasympathetic responses in patients after myocardial infarction. *Am J Cardiol* 1976; **37:** 1013–8.

4 Kirby BJ. Circulatory reflexes in myocardial infarction. *Br Heart J* 1977; **39:** 168–72.

5 Roland JM, Wilcox RG, Banks DC, Edwards B, Fentem PH, Hampton JR. Effect of beta-blockers on arrhythmias during six weeks after suspected myocardial infarction. *Br Med J* 1979; **ii:** 518–21.

6 Hansson L, Westerlund A, Åberg H, Karlberg BE. A comparison of the antihypertensive effect of atenolol (ICI 66 082) and propranolol. *Eur J Clin Pharmacol* 1976; **9:** 361–5.

7 Fentem PH, Greenfield ADM. Measurements of blood flow. In: Atkins H, ed. *Measurement and precision in surgery*. Oxford: Blackwells, 1969: 189–201.

8 Bennett T, Farquhar IK, Hosking DJ, Hampton JR. Assessment of methods for estimating autonomic nervous control of the heart in patients with diabetes mellitus. *Diabetes* 1978; **27:** 1167–74.

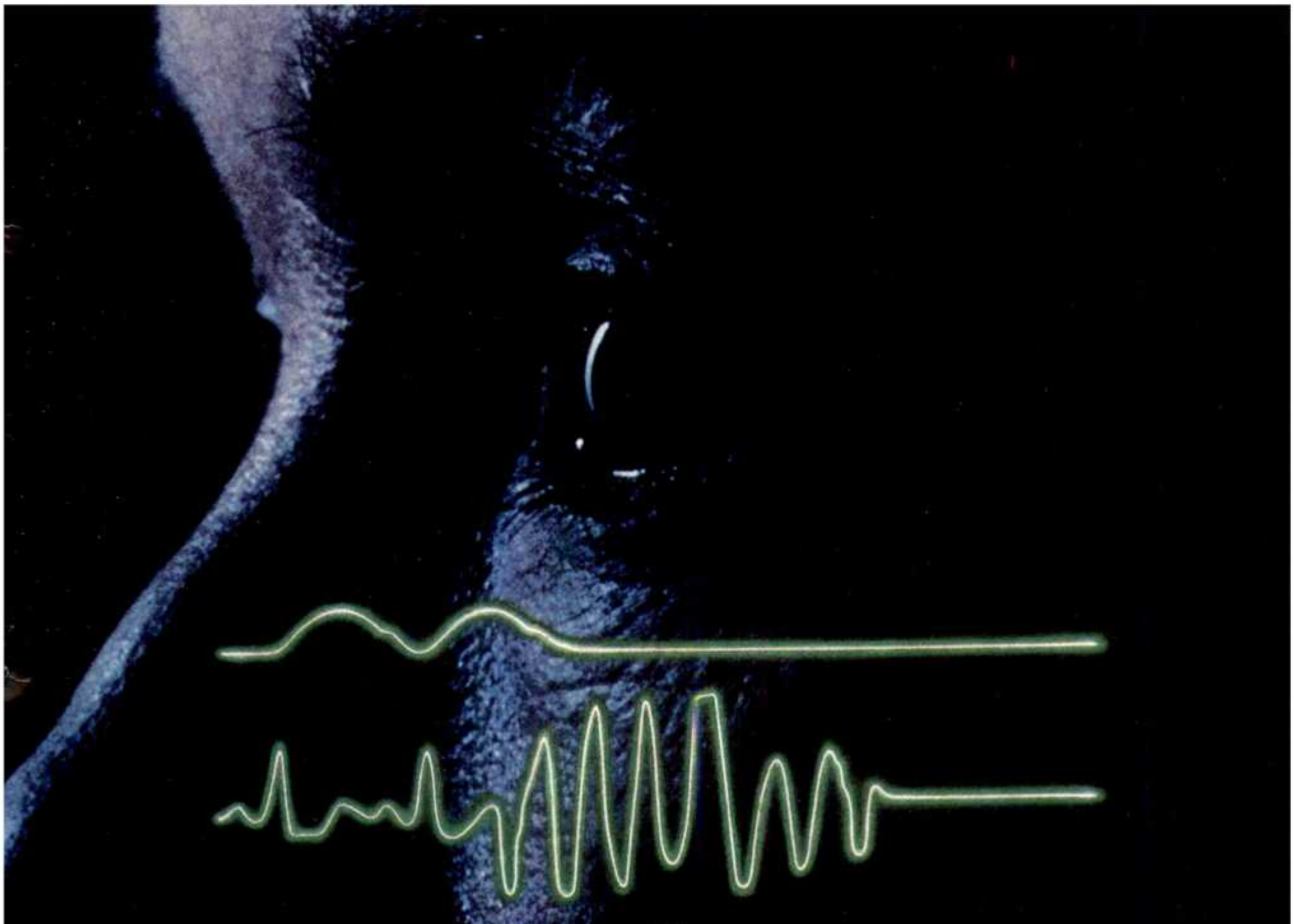
9 Brown E, Goei JS, Greenfield ADM, Plassaras GC. Circulatory responses to simulated gravitational shifts of blood in man induced by exposure of the body below the iliac crests to subatmospheric pressure. *J Physiol (Lond)* 1966; **183:** 607–27.

10 Brod J, Cachovan M, Bahlmann J, *et al.* Haemodynamic response to an acute emotional stress (mental arithmetic) with special reference to the venous side. *Aust NZ J Med* 1976; **6,** suppl 2: 19–25.

11 Bennett T, Hosking DJ, Hampton JR. Baroreflex sensitivity and response to the Valsalva manoeuvre in subjects with diabetes mellitus. *J Neurol Neurosurg Psychiatry* 1976; **39:** 178–83.

12 Bennett T, Hosking DJ, Hampton JR. Cardiovascular responses to graded reductions of central blood volume in normal subjects and in patients with diabetes mellitus. *Clin Sci Mol Med* 1980; **58:** 193–200.

13 Bennett T, Hosking DJ, Hampton JR. Cardiovascular reflex responses to apnoeic face immersion and mental stress in diabetic patients. *Cardiovasc Res* 1976; **10:** 192–9.



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was withdrawn. Gradual discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Hyperuricae has been observed with thiazides but clinical gout is rare. Photosensitivity, anaphylactic reactions and depression of the formed elemer of the blood have been reported rarely with thiazides. **OVERDOSAGE** If excessive bradycardia (and/or hypotension) occurs, atropine 0.5 to 2.0mg should be given intravenously, immediately followed, if necessary, by a beta receptor stimulating agent, such as isoprenali intravenously 5mcg/minute up to 25mcg initially. **LEGAL CATEGORY** POM. **PACKAGE QUANTITIES SOTAZIDE tablets**: units of 28 – blister strips of 14 tablets with 2 strips per carton. **BASIC NHS PRICE** Sotazide compliance pack of 28 tablets £6.78. **PRODUCT LICENCE NUMBER SOTAZIDE tablets**: 0125/0113.

References 1. Kannel WB, Doyle JT, McNamara PM et al. Precursors of sudden coronary death. *Circulation* 1975; 51(4): 606-613. **2.** Sundquist H, Anttila M, Simon A, Reich JW. Comparative bioavailability and pharmacokinetics of sotalol administered alone and in combination with hydrochlorothiazide. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 565-570. **3.** Jaattela A. The combination of sotalol and hydrochlorothiazide in the treatment of hypertension. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 557-564. **4.** Basson W, Myburgh DP. Synergi of a beta blocker and a diuretic in the once-a-day treatment of essential hypertension. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 571-578. **5.** Reynaert J. Once-a-day treatment with sotalol and hydrochlorothiazide in patients with essential hypertension. *J Clin Pharmacol* 19 19(8/9, pt 2): 579-583. **6.** Montalvo HJ. Sotalol/hydrochlorothiazide in geriatric hypertensive patients. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 584-590. *Trademark. Authorised User. Further information is available to the medical profession on request.

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References

1. Nayler, W.G. *Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
2. Flameng, W. *et al. Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
3. Detry, J.M.R. *et al. Eur. J. Cardiol.* **4,** 165, 1976.
4. Gobel, F.L. *et al. Am. J. Cardiol.* **37,** 139, 1976.
5. Jenkins, M.D. *et al. Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
6. Bloem, Th.J.J.M. *et al. Clin. Cardiol*, **2,** 407, 1979.
7. Shapiro, W. *Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
8. Nordstrom, L.A. *Chest*, **74,** 50, 1978.

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Br Heart J 1980; **44**: 271–9

Site and severity of coronary narrowing and infarct size in man

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SUMMARY The relation between the site and severity of coronary artery lesion and infarct size was investigated in 59 patients with acute myocardial infarction. All patients had no prior myocardial infarction and had at least one significant coronary narrowing ($\geq 75\%$) in one of the major coronary arteries or in the first diagonal branch. Left ventriculography and selective coronary arteriography were performed on average 2·2 months after the onset of infarction to identify the site and severity of coronary narrowing and to assess the extent of the non-contracting segment (akinetic, dyskinetic, or aneurysmal). Thirty-four of 59 patients were studied enzymatically and total CK released was taken as an indication of infarct size.

Non-contracting segment and total CK released in group L-I (narrowing proximal to the first diagonal branch) were significantly larger than those in group L-II (a coronary lesion distal to the branch). The data also indicate that the perfusion area of the first diagonal branch is as large as that of the left anterior descending artery below the first diagonal branch. In contrast to left anterior descending artery disease, the involvement of the right ventricular branch did not significantly influence the infarct size. However, infarct size was significantly larger in eight patients with the left ventricular branch of the right coronary artery supplying the predominantly large area of posterior wall of the left ventricle than in nine patients with small left ventricular branches It was also shown that the severity of coronary narrowing does not correlate with the infarct size in either left anterior descending or right coronary artery disease.

Recently many attempts have been made to reduce the infarct size in patients with acute myocardial infarction since infarct size determines very largely the cardiac function and prognosis.[1–3] One of the major factors related to infarct size and cardiac performance, however, is the coronary artery involved as well as the site of the coronary lesions, both of which have been thought to influence the ischaemic area directly.[4 5] Though the relation between the site of the coronary occlusion and the infarct size has been studied experimentally,[6] this relation in patients with acute myocardial infarction remains to be elucidated. Histologically assessed infarct size in postmortem studies does not reflect the infarct size in the acute phase; it may be modified during the postinfarction period, sometimes it may decrease during the healing process, and sometimes increase during clinically undetectable extension of ischaemia. In this study the relation between infarct size, which was assessed from the total CK released or from the extent of non-contracting segment in the left ventriculograms, and the site and severity of the coronary lesions which were evaluated by selective coronary arteriography undertaken within six months (average 2·2 months) after the onset of infarction, was investigated in 59 patients with acute myocardial infarction.

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Subjects and methods

Seventy-one patients (average age 51·6 years) with acute primary myocardial infarction, who had left ventriculography and selective coronary arteriography within six months of the attack, were studied. Four patients whose left ventriculograms were not suitable for quantitative evaluation of wall motion

Table 1 *Involved coronary artery and infarct size in 59 patients with significant (≥75%) coronary narrowing*

With non-contracting segment		*Without non-contracting segment*	
Infarct site and involved vessel	*No. of patients*	*Infarct site and involved vessel*	*No. of patients*
Anterior myocardial infarction	30	Anterior myocardial infarction	
Left anterior descending group L– I	10	Left anterior descending	3
group L–IIa	9		
group L–IIb	11		
Inferior myocardial infarction	19	Inferior myocardial infarction	
Right coronary artery group R–L	8	Right coronary artery	2
group R–S	9		
Left circumflex	2	Left circumflex	0
Lateral myocardial infarction		Lateral myocardial infarction	
First diagonal branch	2	First diagonal branch	3
Total	51	Total	8

and eight patients who had insignificant coronary narrowing (<75% in diameter) were excluded from this study (Table 2). The remaining 59 patients (52 men and seven women) with an average age of 52·9 years, consisted of 33 with anterior infarction, 21 with inferior infarction, and five with lateral infarction (Tables 1 and 3). In these 59 patients, 44 had single vessel disease. In 15 patients with multiple vessel disease, a coronary lesion whose location corresponded to the electrocardiographic changes in standard 12 leads, was studied in relation to the infarct size. Total CK released was obtained in 34 of 59 patients as an indication of infarct size by the method of Sobel *et al.*[7] modified by Norris *et al.*[8] Peripheral venous blood for CK determination was drawn every four hours for the first 24 hours and then at six-hourly intervals until serum CK activity returned to near normal levels.[9] The total CK released which directly reflects the infarct size was calculated as follows:

$$\int_0^t f(t)dt = E(t) + K \int_0^t E(t)dt$$

where, E(t) represents the instantaneous serum CK activity after subtracting the individual basal serum CK activity and f(t) is the appearance rate of myocardial CK released from the injured myocardium into the circulation. The disappearance rate (K) was obtained individually from the terminal portion of the disappearance curve (E(t)) plotted semilogarithmically.

All patients had left ventriculography and selective coronary arteriography on average 2·2 months (one to six months) after the onset of infarction. Left ventriculography was performed after right and left cardiac catheterisation with premedication by intramuscular injection of hydroxyzine 25 mg. After the measurement of cardiac output by the dye dilution method, a 30° right anterior oblique (RAO) projection of the left ventriculogram or both RAO and left anterior oblique (LAO) projections were obtained by injection of 40 to 50 ml sodium diatrizoate (Urografin 76), with exposure of 60 frames/s on 35 mm cine-film by Cardiodiagnost (Phillips Co).

Table 2 *Infarct site in eight patients without significant coronary narrowing*

With non-contracting segment		*Without non-contracting segment*	
Infarct site	*No. of patients*	*Infarct site*	*No. of patients*
Anterior myocardial infarction	2	Anterior myocardial infarction	1
Inferior myocardial infarction	0	Inferior myocardial infarction	3
Lateral myocardial infarction	0	Lateral myocardial infarction	2
Total	2	Total	6

Ventricular wall motion was evaluated and classified according to the criteria of the American Heart Association[10]: hypokinesis (reduced), akinesis (none), dyskinesis, and aneurysm of left ventricle. The segment of abnormal contraction was also expressed according to this classification: region 1 to 5 in RAO projection and region 6 to 7 in LAO projection. In order to identify the akinetic, dyskinetic, and aneurysmal segment, end-diastolic

Table 3 *Number of involved coronary arteries in 59 patients with significant (≥75%) narrowing*

	Myocardial infarction		
	Anterior	*Inferior*	*Lateral*
Single vessel disease	29	13	2
Double vessel disease	4	6	3
Triple vessel disease	0	2	0
Total	33	21	5

and end-systolic silhouettes of the left ventricular chamber for a single beat were superimposed and the ratio of the extent of the non-contracting segment (akinetic, dyskinetic, or aneurysmal segment) of the ventricle to the total end-diastolic circumference was calculated as the non-contracting segment[11] (see Fig. 1). In patients who had left ventriculography in two projections (RAO and LAO), the non-contracting segment was calculated as a mean value on these two projections. Segment of hypokinesis was not included in the non-contracting segment because the extent of this disorder of movement cannot be quantitatively assessed.

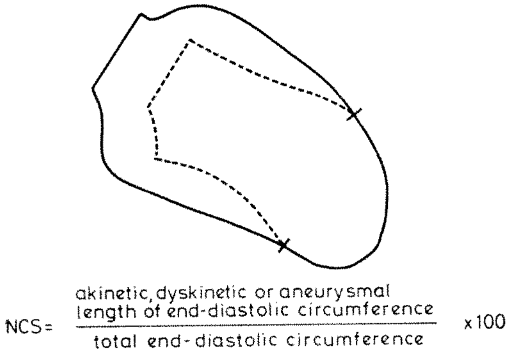
NCS = akinetic, dyskinetic or aneurysmal length of end-diastolic circumference / total end-diastolic circumference x100

Fig. 1 *Measurement of the extent of the non-contracting segment.*

Ten patients who had a significant ($\geqslant 75\%$ in diameter) narrowing proximal to the first diagonal branch and also had a non-contracting segment in the anterior wall or apical portion of the left ventricle were included in group L–I. Twenty patients who had the non-contracting segment in the anterior wall or apical portion but showed a significant narrowing distal to the first diagonal branch were included in group L–II. The latter group was further divided into two groups: group L–IIa (nine patients) with the coronary lesion between the origin of the first diagonal branch (DX_1) and that of the first septal branch (S_1), and group L–IIb (11 patients) with the lesion distal to the position of the first septal branch (see Table 1 and Fig. 2).

In right coronary artery disease nine patients with the narrowing proximal to the right ventricular branch (RV in Fig. 2) were included in group R–I, and eight patients with the coronary lesion in the distal portion below the right ventricular branch were classified as group R–II. Moreover, these 17 patients with right coronary artery disease were divided into two groups according to the relative size of area in the posterior wall of the left ventricle supplied by the right coronary artery. Group R–L included eight patients where the posterior wall of the left ventricle was predominantly (more than two-thirds of the area) supplied by the left ventricular branch of the right coronary artery and the posterolateral branch of the left circumflex artery was small or rudimentary. One patient with a large posterior descending branch distributed to the apical area of the left ventricle was also included in this group. Group R–S included nine patients with a small left ventricular branch which perfused less than two-thirds of the posterior wall.

In this series, 19 of 21 patients with inferior infarction had significant narrowing in the right coronary artery, all of them showing a predominant

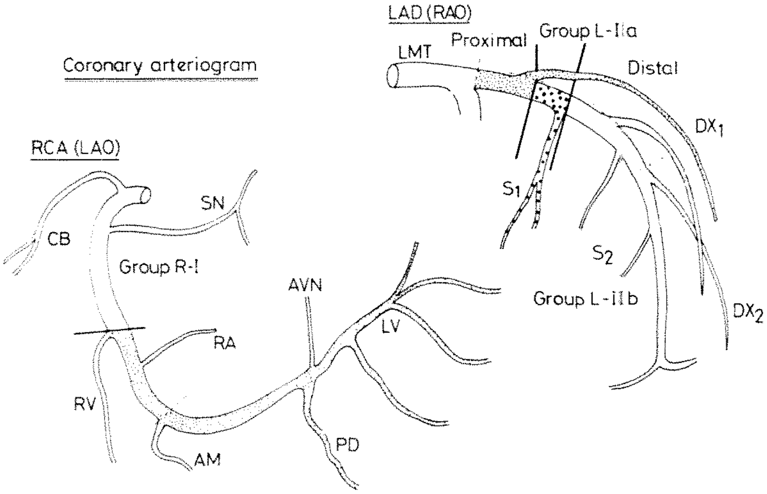

Fig. 2 *Location of the coronary lesion and classification of groups. Proximal is group L–I; and distal is group R–II.*

Table 4 *Values in six patients with single lesion in first diagonal branch (lateral infarction)*

Case no.	*Age (y)*	*Sex*	*Coronary arteriogram findings (%)*	*Abnormal motion of ventricular wall*	*Total CK (IU/ml)*	*Non-contracting segment (%)*
1	54	M	Left anterior descending 50 First diagonal branch 50	Hypokinesis 2, 3	691	—
2	45	M	First diagonal branch 99	Hypokinesis 2, 3	—	—
3	55	F	First diagonal branch 75	Hypokinesis 2, 7	333	—
4	42	M	First diagonal branch 100	Hypokinesis 2	—	—
5	54	F	First diagonal branch 100	Dyskinesis 2, 3	771	19·2
6	62	M	First diagonal branch 100 Left circumflex 90	Dyskinesis 2, 3 Hypokinesis 7	956	17·7

right coronary artery. The remaining two patients had an occlusion in the left circumflex artery. Five patients had significant narrowing in the first diagnonal branch and all of them had lateral infarction (Tables 1 and 4). One patient with less than 75 per cent coronary narrowing but with a hypokinetic segment in regions 2 and 3 is also included in the lateral infarction group (Table 4).

Results

(1) LOCATION AND SEVERITY OF CORONARY NARROWING IN LEFT CORONARY ARTERY AND INFARCT SIZE

All 33 patients with significant narrowing in the left anterior descending artery showed impaired wall motion in the anterior wall or apex of the left ventricle and 30 of these patients showed akinesis, dyskinesis, or aneurysm of the anterior wall. Mean non-contracting segment in groups L–I, L–IIa, and L–IIb were 35·7 ±1·3, 26·4 ±3·0, and 21·4 ±2·7 per cent, respectively, indicating that the extent of infarction in group L–I is significantly larger than in groups L–IIa and L–IIb ($p < 0·01$, see Table 5). These groups showed insignificant differences in age and the incidence of collaterals, suggesting that the difference in the extent of the non-contracting segment is primarily the result of the difference in the site of the coronary lesion. The total CK released also showed that the infarct size in group L–I (total CK 1510 ±190 IU/ml, n=7) was significantly larger ($p < 0·01$) than that in group L–IIa (total CK 765 ±50·4 IU/ml, n=5), or in group L–IIb (total CK 841 ±49·5 IU/ml, n=4), though there was no difference in infarct size between groups L–IIa and L–IIb. These results suggest that a coronary lesion proximal to the first diagonal branch causes a large infarct and that involvement of the first septal branch may not primarily influence the infarct size. Fig. 3 and 4 show the difference in the extent of the non-contracting segment and the total CK released between groups L–I and L–II. These figures show the significant difference ($p < 0·01$) in infarct size between those with and those without involvement of the first diagonal branch; the mean total CK released in patients with a coronary lesion proximal to the first diagonal branch is approximately twice as great as that in patients with distal coronary lesions in the left anterior descending artery. This indicates that the size of the perfusion area of the first diagonal branch is almost similar to that of the left anterior descending artery distal to the first diagonal branch.

Six patients had narrowing only in the first diagonal branch (Table 4), including one patient (case 1) who was excluded from the statistical analysis because of the absence of significant coronary narrowing (≥75%). All had lateral infarction and four patients showed hypokinesis in region 2, while the remaining two had dyskinetic movement in the same region. The extent of the non-contracting segments in these two patients was 19·2 and 17·7 per cent and the mean total CK

Table 5 *Location of coronary lesion in left anterior descending artery and infarct size (mean ±SE)*

Group	*No. of patients*	*Mean age (y)*	*Incidence of collateral (%)*	*Non-contracting (%)*		*Total CK (IU/ml)*
				RAO	*RAO+LAO*	
L– I	10	53·8	40	35·7 ±1·3	36·8 ±2·2 (n=7)	1510 ±190 (n=7)
				*	*	*
L–IIa	9	53·0	56	26·4 ±3·0	28·8 ±3·5 (n=8)	765 ±50·4 (n=5)
				NS *	NS *	NS *
L–IIb	11	51·0	36	21·4 ±2·7	23·8 ±4·5 (n=6)	841 ±49·5 (n=4)

*$p < 0·01$.

released obtained in four patients studied was 688 IU/ml, which was nearly equal to the difference (711 IU/ml) in the mean total CK released in group L–I and L–II; this confirms the result above that the size of the perfusion area of the first diagonal branch is as large as that of the distal left anterior descending artery.

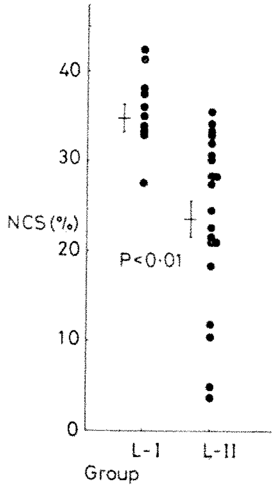

Fig. 3 *Location of the coronary lesion in the left anterior descending artery and the extent of the non-contracting segment (NCS). Group L–I includes the patients with a significant (≥75%) narrowing proximal to the first diagonal branch and group L–II includes the patients with a coronary lesion (≥75%) distal to this branch.*

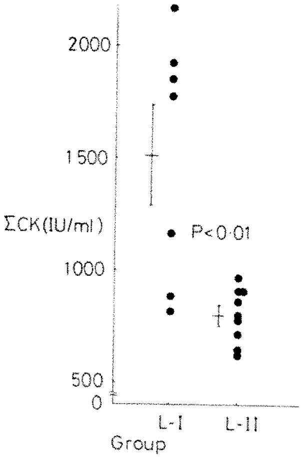

Fig. 4 *Location of the coronary lesion in the left anterior descending artery and the total CK released (ΣCK). (Groups L–I and L–II are the same as those in Fig. 3.)*

In two patients with a significant lesion in the left circumflex artery, one had the balanced type of coronary distribution and the other had a predominant left coronary artery. In the former patient the extent of the non-contracting segment was 30·2 per cent and total CK was 976 IU/ml, and the latter had hypokinesis in region 2 with a total CK of 884 IU/ml.

Fig 5 depicts the relation between the severity of coronary narrowing and the extent of the non-contracting segment in each of the groups L–I and L–II. It shows no significant difference in the extent of infarction resulting from the difference in the severity of narrowing.

(2) LOCATION AND SEVERITY OF NARROWING IN RIGHT CORONARY ARTERY AND INFARCT SIZE

The non-contracting segment (akinesis, dyskinesis, or aneurysm) was observed in 17 of 19 patients with significant narrowing in the right coronary artery. The mean non-contracting segments in group R–I (proximal) and R–II (distal) were 20·4±2·1 per cent and 23·7±3·1 per cent, respectively (Fig. 6). The mean total CK in these two groups also showed no significant difference: 1238±59·3 IU/ml in group R–I and 1070±104 IU/ml in group R–II (Table 6). These results suggest

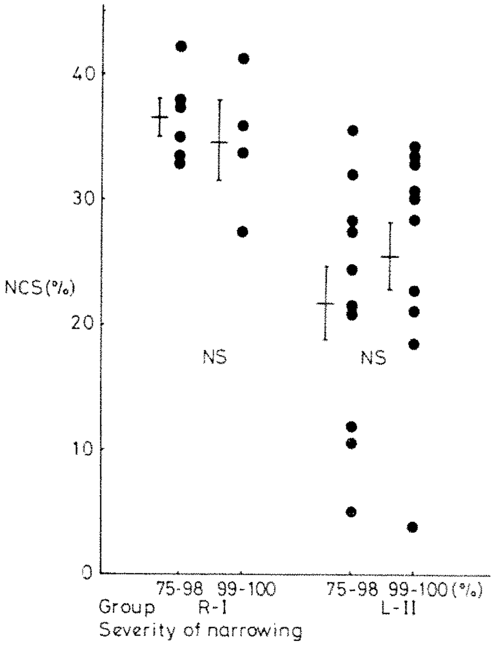

Fig. 5 *Severity of coronary narrowing and extent of the non-contracting segment (NCS). (Groups L–I and L–II are the same as in Fig. 3.)*

Table 6 *Location of coronary lesion in right coronary artery and infarct size (mean ±SE)*

Group	*No. of patients*	*Mean age (y)*	*Incidence of collateral (%)*	*Non-contracting segment (%)* *RAO*		*Non-contracting segment (%)* *RAO+LAO*		*Total CK (IU/ml)*	
R- I	9	51·8	78	20·4 ±2·1	NS	18·9 ±2·1 (n=7)	NS	1238 ±59·3 (n=4)	NS
R–II	8	56·9	75	23·7 ±3·1		23·8 ±4·6 (n=5)		1070 ±104 (n=7)	

that infarct size is not influenced by involvement of the right ventricular branch which is the main branch of the right coronary artery. The mean non-contracting segments and total CK in group R–L (where the left ventricular branch predominantly perfuses the posterior wall of the left ventricle), however, were 27·6 per cent and 1297 IU/ml, respectively, which are significantly larger than those in group R–S (where only a minor part of the posterior wall is perfused by the left ventricular branch of the right coronary artery): 18·2 per cent for the mean non-contracting segment and 920 IU/ml for the mean total CK (Fig. 7). This indicates that the size of the perfusion area of the right coronary artery in the left ventricle mainly determines the infarct size in patients with right coronary artery disease.

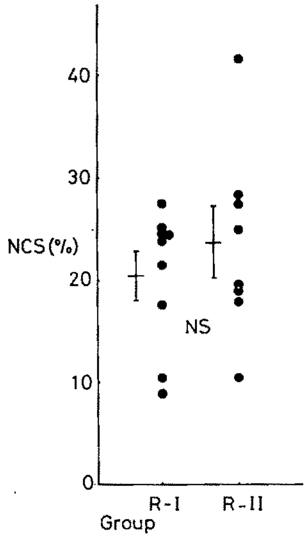

Fig. 6 *Location of the lesion in the right coronary artery and the extent of the non-contracting segment (NCS). In group R–I the narrowing of the right coronary artery is proximal to the right ventricular branch and in group R–II distal to the right ventricular branch.*

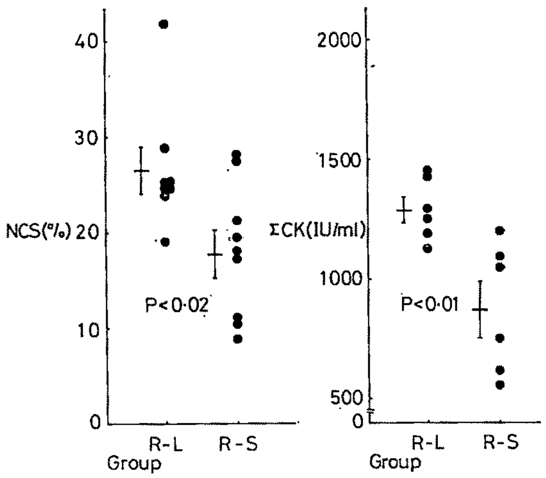

Fig. 7 *Distribution area of the right coronary artery and infarct size (NCS and ΣCK). The patients in group R–L had the large left ventricular branch of the right coronary artery supplying the predominantly large area of the posterior wall of the left ventricle. The patients in group R–S had a minor left ventricular branch which supplied less than one-third of the posterior area of the left ventricle.*

Fig. 8 shows the relation between the severity of coronary narrowing and the extent of the non-contracting segment. There was no significant difference in the mean non-contracting segment between the patients with subtotal or complete occlusion in the right coronary artery. As shown in the case of the left anterior descending artery, the severity of narrowing in the right coronary artery did not influence the infarct size.

(3) LOCATION OF CORONARY LESION AND CARDIAC FUNCTION

Table 7 shows the pertinent haemodynamic indices in patients with significant narrowing in the left anterior descending artery (group L–I and L–II) and the right coronary artery (groups R–L and R–S). In 30 patients with left anterior descend-

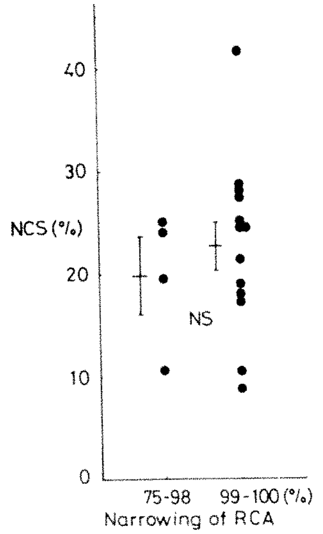

Fig. 8 *Severity of coronary narrowing in the right coronary artery and the extent of the non-contracting segment (NCS).*

ing artery disease, the mean ejection fractions in group L–I (proximal) and L–II (middle and distal) were 32·1 ±3·1 and 46·8 ±2·1 per cent, respectively. Though the cardiac index showed no significant difference between the two groups, the left ventricular end-diastolic volume was significantly larger in group L–I, suggesting that the cardiac index was compensated by the Starling mechanism because the heart rate in these groups did not show a significant difference (group L–I: 78·8 ±4·9 beats/min; group L–II: 72·0 ±4·4 beats/min). This haemodynamic compensation by the Starling mechanism was also seen in groups R–L and R–S with right coronary artery disease (see also Table 7). Only left ventricular end-diastolic volume showed a significant ($p < 0{\cdot}01$) difference between groups R–L and R–S, while the ejection fraction, cardiac index, and heart rate showed no significant difference between these two groups.

Discussion

The present study shows that the site of the coronary lesion in the left anterior descending artery is the major determinant of infarct size, and that involvement of the first diagonal branch results in a large infarction. In contrast to the left anterior descending artery, in right coronary artery disease the variation of the perfusion area of the right coronary artery in the posterior wall of the left ventricle was shown to be a major determining factor of infarct size, and the involvement of the right ventricular branch did not significantly influence the extent of infarction. It was also shown that the severity of coronary narrowing assessed by coronary arteriography does not correlate with the infarct size both in left anterior descending artery and right coronary artery disease.

Although the close relation of the involved major coronary artery to the site of the myocardial lesion has been well established,[12 13] the size of the perfusion area of its branches remains to be elucidated. Fulton,[14] and Mitchell and Schwartz[15] described the pathological features of coronary arteries associated with large or small infarcts. Some previous investigators also reported the relative size of the myocardial mass perfused by each of the major coronary arteries in the heart at necropsy.[16–18] Infarct size, however, may be modified by many factors such as haemodynamic conditions, clinical interventions, presence of collaterals before myocardial infarction, and the tolerance of the myocardium to ischaemia.[3] Therefore, the relation of infarct size and the site of the coronary lesion should preferably be investigated clinically. We considered the significant (≥75%) coronary narrowing, which corresponded to the infarct site judged from the electrocardiographic changes in standard 12-leads, as the cause of the infarction. This assumption is acceptable because narrowing of more than 75 per cent was observed in coronary arteriograms of almost all patients with acute myocardial infarction[13 19] and the site of the

Table 7 *Cardiac function in patients with left anterior descending artery disease and right coronary artery disease (mean ±SE)*

Group	*Ejection fraction (%)*		*Cardiac index (l/min per m²)*		*Left ventricular end-diastolic volume (ml/m²)*		*Heart rate/min*	
L–I	32·1 ±3·1	NS	2·8 ±0·3	NS	143 ±11·8	*	78·8 ±4·9	NS
L–II	46·8 ±2·1		2·7 ±0·2		113 ±5·3		72·0 ±4·4	
R–L	52·1 ±3·8	NS	2·6 ±0·2	NS	130 ±9	*	72·4 ±11·2	NS
R–S	53·7 ±2·0		2·4 ±0·3		88 ±11		65·5 ±3·1	

* $p < 0{\cdot}01$.

maximal stenosis or occlusion of the coronary artery had also been reported to correspond to the infarct site.[20]

In this study the figures for mean total CK released in patients with proximal left anterior descending artery disease, left circumflex disease, and right coronary artery disease were 1510, 930, and 1131 IU/ml, and their relative percentages were 42·2, 26·0, and 31·7, respectively. Kalbfleisch and Hort[16] reported that the relative perfusion areas of these three coronary arteries in the human heart were 41·5 per cent left anterior descending, 22·3 per cent left circumflex, and 36·2 per cent right coronary artery. These values are similar to those of the present study described above. The infarct size in right coronary artery disease may be smaller, however, than the perfusion area of the right coronary artery because right ventricular infarction is much less frequent than left ventricular infarction by right coronary artery involvement. This may account for the smaller value (31·7%) of relative total CK in right coronary artery disease in this study than the 36·2 per cent of Kalbfleisch's data. Ahmed *et al.*[17] also reported that the perfusion area of the left coronary artery was almost equal to that of the right coronary artery, confirming our results obtained in clinical study.

In this study also the involvement of the first diagonal branch was found to influence directly the extent of the non-contracting segment. Since the extent of the non-contracting segment represents the ratio of the segment length of the non-contracting portion to the circumference of the left ventricle, the relative area of the non-contracting portion should be represented by the squared value of the non-contracting segment. The ratio of the non-contracting area (squared non-contracting segment) in group L–I (with the lesion proximal to the first diagonal branch) to that in group L–II (with the lesion distal to the first diagonal branch) was 1·0:0·46. This indicates that the perfusion area of the first diagonal branch is as large as that of the distal portion of the left anterior descending artery below the first diagonal branch. On the other hand, the mean total CK released in patients with only left circumflex artery disease was 688 ± 113 IU/ml, which is also as large as the mean total CK (799 ± 38 IU/ml) in group L–II with distal left anterior descending lesion. These results strongly suggest that the first diagonal branch has a substantially large perfusion area in the left ventricle. Mullen *et al.*[21] also emphasised the great contribution of the first diagonal branch to the formation of ventricular aneurysm which often accompanied a large infarction. In contrast to the first diagonal branch, the contribution of the first septal branch to the infarct size was thought to be small. It has been believed that the septal branch supplies blood only to the anterior half of the interventricular septum, and, therefore, a single lesion in the left anterior descending artery with complete necrosis of the septal wall is rare.[22] In this study most of the patients with the coronary lesion proximal to the septal branch have no other coronary lesions, and this may account for the lower contribution of the first septal branch to infarct size.

In contrast to left anterior descending disease, the infarct size in right coronary artery disease was not directly dependent upon whether the major branch, that is the right ventricular branch, was involved or not, but it was greatly influenced by the distribution balance of the right coronary artery and left circumflex artery in the posterior wall of the left ventricle. Kalbfleisch and Hort[16] also pointed out the great variation in size of the area perfused by the right coronary artery, ranging from 16·4 to 46·4 per cent of the total area, depending upon the predominance of vascular distribution, that is left coronary or right coronary artery type. In this series the patients in group R–L with a large left ventricular branch of the right coronary artery had the larger infarct (non-contracting segment: 27·6%, total CK: 1297 IU/ml) than those in group R–S with a large posterolateral branch of the left circumflex (non-contracting segment: 18·2%, total CK 920 IU/ml). Contrary to this, the site of the coronary lesion in the right coronary artery did not influence infarct size and nor did involvement of the right ventricular branch; this indicates indirectly that right ventricular infarction is much less frequent than left ventricular infarction. Though the relation between the site of the coronary lesion and infarct size was elucidated in this study, it should be noted that the perfusion area may be different from the infarct size. Schaper *et al.*[23] described the perfusion area as being usually larger than the infarct area because of the collateral flow supplying the surrounding area of the infarction. In our series, however, it seems likely that the collaterals do not influence the infarct size because there were no significant differences in the incidence of collaterals between groups L–I and L–II, and also between groups R–L and R–S.

As one can estimate from the significant difference in infarct size between groups L–I and L–II, the ejection fraction was significantly smaller in group L–I than in group L–II. Cardiac index, however, was not reduced in group L–I; it may be a result of the compensatory mechanism of the Starling effect since left ventricular end-diastolic volume was larger in group L–I than in group L–II, while heart rate was similar in these two groups

(Table 7). On the other hand, in right coronary artery disease the ejection fraction in groups R–L and R–S showed no significant difference though infarct size in group R–L was significantly larger than that in group R–S. This paradoxical finding is probably a result of the smaller contribution of the inferior wall than of the anterior wall to the left ventricular pump function.[11]

There was no correlation between the severity of coronary narrowing and infarct size. This result is compatible with the previously reported results in patients with acute myocardial infarction[13] though the cross-sectioned area of the coronary artery without any coronary lesions closely correlates with the perfusion area.[18–24] Taking the secondary thrombosis after the infarction and the recanalisation of coronary occlusion into account, there may be no correlation between the severity of coronary narrowing and infarct size. The relation between the results on the site of the coronary lesion and infarct size shown in this study, however, should be of clinical importance in evaluating the therapeutic interventions and also in estimating prognosis for the patients.

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References

1 Pfeffer MA, Pfeffer JM, Fishbein MC, *et al.* Myocardial infarct size and ventricular function in rats. *Circ Res* 1979; **44:** 503–12.

2 Feild BJ, Russell RO Jr, Moraski RE, *et al.* Left ventricular size and function and heart size in the year following myocardial infarction. *Circulation* 1974; **50:** 331–9.

3 Maroko PR, Kjekshus JK, Sobel BE, *et al.* Factors influencing infarct size following experimental coronary artery occlusions. *Circulation* 1971; **43:** 67–82.

4 Corr PB, Pearle DL, Hinton JR, Roberts WC, Gillis RA. Site of myocardial infarction. A determinant of the cardiovascular changes induced in the cat by coronary occlusion. *Circ Res* 1976; **39:** 840–7.

5 Burstein J. Myocardial infarction. Acute course and prognosis in one hundred and twenty-seven cases of varied extent and localization electrocardiographically determined with the aid of multiple unipolar leads. *Acta Med Scand* 1953; suppl: **285,** 1–83.

6 Capone RJ, Most AS, Sydlik PA. Precordial ST segment mapping. A sensitive technique for the evaluation of myocardial injury? *Chest* 1975; **67:** 577–82.

7 Sobel BE, Bresnahan GF, Shell WE, Yoder RO. Estimation of infarct size in man and its relation to prognosis. *Circulation* 1972; **46:** 640–8.

8 Norris RM, Whitlock RML, Barratt-Boyes C, Small CW. Clinical measurement of myocardial infarct size. Modification of a method for the estimation of total creatine phosphokinase release after myocardial infarction. *Circulation* 1975; **51:** 614–20.

9 Inoue M, Hori M, Fukui S, *et al.* Evaluation of evolution of myocardial infarction by serial determination of serum creatine kinase activity. *Br Heart J* 1977; **39:** 485–92.

10 Austen WG, Edward JE, Frye RL, *et al.* AHA Committee report. A reporting system on patients evaluated for coronary artery disease. *Circulation* 1975; **51** (4): 6–40.

11 Hori M, Inoue M, Fukui S, *et al.* Correlation of ejection fraction and infarct size estimated from the total CK released in patients with acute myocardial infarction. *Br Heart J* 1979; **41:** 433–40.

12 Ratshin RA, Massing GK, James TN. Clinical significance of the location of acute myocardial infarction. In: Cordy E, Swan HJC, eds. *Myocardial infarction.* Baltimore: Williams & Wilkins, 1973: 77–85.

13 Proudfit WL, Shirey EK, Sones FM Jr. Selective cine coronary arteriography. Correlation with clinical findings in 1000 patients. *Circulation* 1966; **33:** 901–10.

14 Fulton WFM. *The coronary arteries. Arteriography, microanatomy, and pathogenesis of obliterative coronary artery disease.* Springfield, Illinois: Charles C Thomas, 1965.

15 Mitchell JRA, Schwartz CJ. *Arterial disease.* Oxford: Blackwell Scientific Publications, 1965.

16 Kalbfleisch H, Hort W. Quantitative study on the size of coronary artery supplying areas postmortem. *Am Heart J* 1977; **94:** 183–8.

17 Ahmed SH, El-Rakhawy MT, Abdalla A, Harrison RG. A new conception of coronary artery preponderance. *Acta Anat (Basel)* 1972; **83:** 87–94.

18 Woods JD. Relative ischaemia in the hypertrophied heart. *Lancet* 1961; **i:** 696–8.

19 Gensini GG, Buonanno C. Coronary arteriography. A study of 100 cases with angiographically proved coronary artery disease. *Dis Chest* 1968; **54:** 90–9.

20 Miyata K, Endo M, Saijo S, *et al.* Clinical study on coronary arteriogram with a reference to electrocardiogram and clinical findings (in Japanese). *Jpn J Angiol* 1972; **12:** 167–71.

21 Mullen DC, Posey L, Gabriel R, Singh HM, Flemma R, Lepley D Jr. Prognostic considerations in the management of left ventricular aneurysms. *Ann Thorac Surg* 1977; **23:** 455–60.

22 James TN. The coronary circulation and conduction system in acute myocardial infarction. *Prog Cardiovasc Dis* 1968; **10:** 410–49.

23 Schaper W, Remijsen P, Xhonneux R. The size of myocardial infarction after experimental coronary artery ligation. *Z Kreislauff* 1969; **58:** 904–9.

24 Baroldi G, Scomazzoni G. Coronary circulation in the normal and pathologic human heart. Washington: US Government Printing Office, American Registry of Pathology, AFIP, 1967.

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Systolic and diastolic time intervals in young diabetics

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SUMMARY Systolic and diastolic time intervals were used to examine left ventricular performance in 22 young diabetic men (mean age 25 years) with no apparent clinical heart disease. Pre-ejection period index (PEPI), left ventricular ejection time index (LVETI), electromechanical systole index (QS_2I), PEP to LVET ratio, the a wave percentage amplitude of the apexcardiogram (a/H% ratio), the rapid filling wave (RFW), and the A_2O interval were obtained in the conventional manner in 22 diabetics and 22 healthy men. The heart rate, diastolic pressure, PEP/LVET ratio, a/H per cent ratio, and A_2O interval were significantly increased and LVET decreased in the diabetic group. QS_2I, PEPI, and RFW did not differ from that in the normal group. Twenty-three per cent of patients had an abnormal systolic time interval, 54 per cent an abnormal diastolic time interval, and 23 per cent had both abnormal intervals. Though these studies provide no definite evidence of a cause, the abnormalities found may reflect a subclinical diabetic cardiopathy.

Cardiac disease has been found to be one of the major complications of diabetes mellitus and for many years was attributed to coronary atherosclerosis. Recently the terms diabetic cardiopathy and diabetic cardiomyopathy have appeared in medical publications.[1] These terms imply the existence of a specific diabetic heart disease, a new nosological entity that has been growing out of several studies performed during the last few years by research workers in diabetes. The assessment of left ventricular function as an index of potential myocardial involvement in diabetic patients without clinical evidence of myocardial ischaemia or other cardiovascular abnormalities has become increasingly important.[2] This study was undertaken to investigate ventricular function as a measure of potential myocardial involvement in young patients with diabetes mellitus. Non-invasive measurement of the systolic and diastolic time intervals provide a reasonable correlation with more direct measures of cardiac performance in the absence of complicating lesions such as valvular or pulmonary disease.[3 4]

Subjects and methods

The function of the left ventricular myocardium was evaluated in 22 diabetic men ranging in age from 20 to 29 years with no apparent clinical heart disease. Subjects were selected who were ambulatory clinic patients or who had recovered at least one week previously from an episode of ketoacidosis that required admission to hospital. All patients had normal blood pressure, were in sinus rhythm, and had no *x*-ray film evidence of cardiac abnormality. However, five patients had signs of left atrial enlargement in their electrocardiograms. Three patients had non-proliferative retinopathy, but none had renal or neurological complications. Each subject was carefully interviewed to exclude from the study subjects with a history of chronic alcoholism. Details of the mean duration of their diabetic status, treatment, blood pressure, and heart rate are listed in Table 1. On the basis of the duration of treatment the diabetic patients were divided into two groups (see Table 3). Group 1: the duration of treatment from three months to five years; group 2: the duration of treatment from five years to 16 years. Twenty-two healthy men (mean age 24 years) served as a control group.

Simultaneous electrocardiogram (lead II), phonocardiogram from the third left intercostal space parasternally, a carotid pulse tracing, or apexcardiogram were recorded during the resting period preceding the measurement of resting blood pressure. The carotid pulse tracing was recorded

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Table 1 *Clinical data of diabetic and healthy men*

	No.	*Age (y)*	*Heart rate/min*	*Pressure (mmHg)*		*Duration of treatment (y)*
				Systolic	*Diastolic*	
Control group	22	24·2 ±3·7	60·1 ±6·4	122·5 ±8·5	76·5 ±4·3	— —
Diabetic group	22	25·2 ±3·5	70·6 ±10·8	126·6 ±9·3	81·3 ±6·3	5·0 4·7
p vs. normal subjects		NS	0·001	NS	0·01	—

NS, not significant ($p < 0·05$). Listed are mean values ± SD.

in the supine position and the apexcardiogram in the left lateral position, both during relaxed expiratory apnoea. All the curves were recorded on a direct writing 8-channel mingograph (EM 82. Siemens Elema AB, Sweden). A pulse/phono transducer 860, with time constant 4·5 s was used. The paper speed was 50 mm/s for the electrocardiogram and 100 mm/s for the other tracing. The apexcardiogram contributed to three of the variables in this study (diastolic time intervals): the a/H per cent ratio, that is the a wave percentage amplitude of the total deflection (H) of the apexcardiogram, the A_2O interval, that is the interval between the aortic component of the second sound and the O-point of the apex curve; the rapid filling wave (RFW) was measured from its beginning (O-point) to the site where the contour deviated toward the horizontal line. Total electromechanical systole (QS_2) was measured from the onset of the QRS complex of the electrocardiogram to the high-frequency component of the second heart sound. Left ventricular ejection time (LVET) was measured from the beginning of the rapid upstroke of the carotid pulse to the nadir of the incisura. The pre-ejection phase was derived by subtracting the left ventricular ejection time from QS_2. The measurements on 10 consecutive beats were determined to the nearest 5 ms and then averaged. Indices of systolic time intervals (QS_2I, LVETI, and PEPI) were derived from the actual measured intervals by applying the regression equation.[5] Resting blood pressure was measured after the non-invasive examination after approximately half an hour's rest; casual blood pressure was measured in the seated position with a mercury manometer and a stethoscope.

Statistical analyses of the results were made by Student's t test.

Results

Diabetic patients had slightly higher levels of heart rate ($p < 0·001$) and arterial diastolic pressure ($p < 0·01$) that were significantly different from normal subjects, but within the normal range (Table 1). The abnormalities of systolic time intervals in the diabetic subjects included a shorter LVETI and an increase in the ratio of PEP to LVET (Table 2) compared with that in the healthy men. Both QS_2I and PEPI were of similar duration to that in the control group. The mean values for the A_2O interval and the a/H per cent ratio were significantly higher in diabetic patients. The rapid filling wave in diabetics did not differ from that in the normal subjects. We did not find any correlations between systolic time intervals or diastolic time intervals and diastolic pressure in the control and diabetic groups. The mean values ±2SD in

Table 2 *Systolic and diastolic time intervals in diabetic and normal subjects (ms)*

	No.	*LVETI*	*PEPI*	*QS_2I*	*PEP/LVET*	*A_2O*	*RFW*	*a/H per cent*
Normal group	22	397·6 ±12·3	117·7 ±12·5	516·2 ±10·2	0·31 ±0·05	106·9 ±7·5	70·5 ±13·8	8·5 ±3·8
Diabetic group	22	388·5 ±14·3	124·9 ±13·8	510·7 ±15·8	0·35 ±0·05	121·1 ±18·9	71·5 ±8·5	11·5 ±4·0
p vs. normal subjects		0·05	NS	NS	0·05	0·01	NS	0·02

Listed are mean values ± SD

LVETI, left ventricular ejection time index; PEPI, pre-ejection period index QS_2I, electromechanical systole index; A_2O interval between aortic component of second sound and O-point of the apex cardiogram; RFW, rapid filling wave; a/H, ratio of a wave amplitude to maximum deflection of the apex cardiogram.

Table 3 *Systolic and diastolic time intervals in diabetics with different duration of treatment*

	QS_2I	$LVETI$	$PEPI$	$PEP/LVET$	A_2O	RFW	a/H *per cent*
Group 1 no. 12	512·0 ±8·2	389·8 ±11·9	128·8 ±13·5	0·33 ±0·04	115·4 ±16·5	70·9 ±7·9	12·7 ±4·3
Group 2 no. 10	509·9 ±18·4	381·4 ±12·3	123·2 ±12·2	0·36 ±0·05	123·4 ±19·9	72·2 ±8·2	9·7 ±2·9
	NS	NS	NS	NS	NS	NS	NS

Listed are mean values ±SD.
For abbreviations see Table 2.

the healthy young men were taken as the normal range for each of the indices. Five diabetics (23%) had at least one abnormal systolic time interval, and 12 (54%) patients had at least one abnormal diastolic time interval. Five patients (23%) had both abnormal systolic and diastolic time intervals. There were no differences in the systolic or diastolic indices in the two diabetic groups between treatment of long or short-term duration (Table 3). Three patients with retinopathy had at least one abnormal systolic or diastolic time interval. Two patients with left atrial enlargement on the electrocardiogram had an abnormal a/H per cent ratio. There was no association between the quality of previous diabetic control and the abnormalities in the systolic or diastolic time intervals.

Discussion

A group of young asymptomatic diabetic patients was selected to evaluate myocardial performance in diabetics without overt cardiac disease. Until recently there have been only a few exact studies of cardiac function in diabetes mellitus. Most of the results available were obtained with the systolic time intervals technique.[6 7] Our study shows a significant shortening of the left ventricular ejection time index ($p < 0{\cdot}05$) and an increase in the ratio between PEP and LVET ($p < 0{\cdot}05$) in the diabetic young men. Though a shorter left ventricular ejection time (LVET) and a higher PEP/LVET ratio is characteristic of the failing heart,[5 8] the moderate abnormalities of these indices in our diabetic patients may not be exclusively related to an abnormality of myocardial contractility. That altered preload may at least contribute to, if not constitute the major determinants of, this preclinical abnormality is suggested by the significantly higher a/H per cent ratio in the diabetic group.[9] Good correlation has been shown between the relative magnitude of the a wave and an index of the left ventricular distensibility[10] or the left ventricular end-diastolic pressure.[9] The interval between the aortic component of the second heart sound and the O-point in the apexcardiogram (A_2O) was longer in diabetic patients ($p < 0{\cdot}01$). Signs of reduced distensibility of the left ventricle were not in parallel with prolongation of the A_2O interval (only one patient with abnormal A_2O interval had abnormal a/H per cent ratio) so that this cannot be the main cause of the prolonged A_2O interval. The prolongation of the A_2O interval could not be explained by differences in heart rate or diastolic pressure (both higher in the diabetic group) since there was no correlation between the A_2O interval and heart rate or diastolic pressure in the control and diabetic groups. Manolas and Rutishauser[4] showed that the A_2O interval was closely correlated with internally measured indices of relaxation and less closely but still significantly with isovolumic contractile indices and ejection fraction in patients with nonobstructive cardiomyopathy. Wikstrand[11] suggested that impaired interrelation between the intensity of the contractile state and the velocity of relaxation may prolong relaxation of the heart and the A_2O interval. Further studies are required to elucidate the reasons for this prolongation of the A_2O interval in diabetic patients. We have found an abnormal systolic time interval in 10 young diabetics and an abnormal diastolic time interval in 17 diabetic patients. Thus, when impairment of left ventricular function is studied at an early stage, interest should be concentrated not only on systole, but also on diastole. Recently Sanderson *et al.*,[12] using echocardiography, reported abnormalities of diastolic function in 17 of 23 young diabetics, most of them with retinopathy. Five of our diabetics had signs of left atrial enlargement in their electrocardiograms, two of whom had an abnormal a/H per cent ratio. However, Zoneraich *et al.*[13] suggested that the P wave abnormalities in diabetics were the result of intra-atrial conduction disturbances or of intra-atrial block and rarely of left atrial enlargement.

It is unlikely that all the abnormalities seen in our study were a result of premature coronary artery disease[14] in view of the youth of our patients (mean age 25 years), lack of symptoms, and different patterns of abnormal systolic or diastolic time intervals. Clearly a spectrum of abnormalities is possible[15] and our results may reflect an interaction between diabetic small-vessel cardiomyopathy, premature onset of coronary artery disease, and diabetic neuropathy.[16] Further studies are needed in order to be able to interpret the significance of the various findings in the diabetic patients.

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References

1 Ledet T, Neubauer B, Christensen NJ, Lundbaek K. Diabetic cardiopathy. *Diabetologia* 1979; **16:** 207–9.
2 Zoneraich S, Zoneraich O, Rhee JJ, Liao C, Patel MM. Electrocardiographic findings in diabetic patients without clinical evidence of heart involvement. *NY State J Med* 1977; **77:** 1254–8.
3 Lewis RP, Rittgers SE, Forester WF, Boudoulas H. A critical review of the systolic time intervals. *Circulation* 1977; **56:** 146–58.
4 Manolas J, Rutishauser W. Relation between apex cardiographic and internal indices of left ventricular relaxation in man. *Br Heart J* 1977; **39:** 1324–32.
5 Weissler AM, Harris WS, Schoenfeld CD. Bedside technics for the evaluation of ventricular function in man. *Am J Cardiol* 1969; **23:** 577–83.
6 Ahmed SS, Jaferi GA, Narang RM, Regan TJ. Preclinical abnormality of left ventricular function in diabetes mellitus. *Am Heart J* 1975; **89:** 153–8.
7 Rubler S, Sajadi RM, Araoye MA, Holford FD. Non-invasive estimation of myocardial performance in patients with diabetes. *Diabetes* 1978; **27:** 127–34.
8 Ahmed SS, Levinson GE, Schwartz CJ, Ettinger PO. Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man. *Circulation* 1972; **46:** 559–71.
9 Voigt GC, Friesinger GC. The use of apexcardiography in the assessment of left ventricular diastolic pressure. *Circulation* 1970; **41:** 1015–24.
10 Gibson TC, Madry R, Grossman W, McLaurin LP, Craig E. The A-wave of the apexcardiogram and left ventricular diastolic stiffness. *Circulation* 1974; **49:** 441–6.
11 Wikstrand J. *Non-invasive assessment of cardiac function.* Goteborg: GOTAB, Kunngalv, 1976: 167–8.
12 Sanderson JE, Brown DJ, Rivellese A, Kohner E. Diabetic cardiomyopathy? An echocardiographic study of young diabetics. *Br Med J* 1978; **i:** 404–7.
13 Zoneraich S, Zoneraich O, Rhee JJ. Left ventricular performance in diabetic patients without clinical heart disease. Evaluation by systolic time intervals and echocardiography. *Chest* 1977; **72:** 748–51.
14 Jarrett J. Diabetes and the heart: coronary heart disease. *Clin Endocrinol Metab* 1977; **6:** 389–402.
15 Regan TJ, Lyons MM, Ahmed SS, *et al.* Evidence for cardiomyopathy in familial diabetes mellitus. *J Clin Invest* 1977; **60:** 885–99.
16 Gundersen HJG, Neubauer B. A long-term diabetic autonomic nervous abnormality. *Diabetologia* 1977; **13:** 137–40.

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Serial measurements of left ventricular dimensions by echocardiography

Assessment of week-to-week, inter- and intraobserver variability in normal subjects and patients with valvular heart disease

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SUMMARY The week-to-week, inter- and intraobserver variation in left ventricular echocardiographic measurements has been studied in 10 normal male volunteers and in five patients with stable valvular disease. A two-way analysis of variance showed no statistically significant variation either from week to week or between observers. Furthermore the within observer variation was minimal. Calculation of the coefficient of variation allowed confidence limits to be applied to each of the six ventricular measurements, thus providing ranges of variation in follow-up studies using M-mode echocardiography.

The development of M-mode echocardiography has allowed much useful information to be obtained about left ventricular structure and function both in health and disease. One application of echocardiography in this regard is in sequential studies to assess the progression or regression of a disease process or the effect of pharmacological intervention. It is therefore important to establish the degree of variation among echocardiographers in their analysis of data. Recently, clear guidelines were suggested for echocardiographic measurements,[1] and, using these guidelines, we have looked at the variations in left ventricular dimensions from week to week for four weeks in 10 normal volunteers and five patients with stable valvular heart disease. We have also assessed the inter- and intraobserver error of three physicians in measuring these echocardiograms.

Subjects and methods

Fourteen normal volunteers and six patients with stable valvular heart disease (on no medication and not showing evidence of cardiac decompensation) were selected for study. Of these, four were excluded from the normal group and one from the group with valvular heart disease at baseline because of technically inadequate tracings. The 10 normal volunteers were all healthy men aged 20 to 35 years (mean 26·8) with no history of cardiac disease. Clinical details of the group with valvular heart disease are described in Table 1.

The echocardiograms were performed with a Smith Kline Ekoline 20A ultrasonoscope and attached strip chart recorder at a paper speed of 50 mm/s in all subjects after 15 minutes' rest. A lead II electrocardiogram was simultaneously recorded. The echocardiographic technique was as described by Henry *et al.*[2] In brief, after a T-scan, a good septal-posterior wall transverse dimension was defined and gain settings were adjusted so that endocardium, epicardium, and both sides of the

Table 1 *Details of five subjects with stable cardiac disease*

Case no.	*Age (y)*	*Sex*	*Clinical diagnosis*
11	46	F	Mitral valve prolapse
12	56	M	Aortic stenosis
13	65	M	Aortic stenosis and regurgitation
14	59	F	Aortic regurgitation
15	50	M	Aortic stenosis

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septum could be clearly seen at the level of the chordae tendineae of the mitral valve apparatus. In this position, all tracings were performed by one of us (GL). At the initial study, the position of the transducer was carefully noted with reference to the interspace and distance from the sternum. The echocardiograms were performed at weekly intervals for four weeks using the same posture and transducer position in each subject as were used in the first recording. The tracings for measurement were chosen and photocopied by one of us (GL) and read independently and in a completely blind manner by the other three of us (called observers A, B, and C). To minimise observer bias in measurement, only five cardiac cycles were included in each tracing. Each observer was provided with a set of guidelines for left ventricular measurements (as shown in Table 2) based on the recommendations of Sahn *et al.*[1]

In all, 60 technically acceptable echocardiograms (Fig.) were performed and each observer measured six indices in each of 70 echocardiograms (including 10 duplicated tracings).

Table 2 *Guidelines for echocardiographic left ventricular measurements*

Left ventricular diastolic internal diameter (LVIDd)
At level of chordae, measure vertical distance from most anterior edge of endocardial echoes to left septum at onset of first deflection of QRS complex of ECG

Left ventricular systolic internal diameter (LVIDs)
Measure vertical distance from most anterior edge of endocardial echoes to left septum at nadir of septal motion (if septal motion is normal), if not, at peak of posterior wall motion

Posterior left ventricular wall thickness (PLVWT)
At onset of first deflection of QRS complex of ECG, measure vertical distance between most anterior edge of endocardial echoes to epicardium at level of chordae

Posterior left ventricular wall amplitude (PLVWA)
Draw horizontal line between most anterior points of left ventricular endocardium in systole, then measure maximal vertical distance from this line to endocardium of LVPW at point just before free wall begins to move anteriorly in systole

Interventricular septal thickness (IVST)
Measure vertical distance from right ventricular side of IVS to its left ventricular side at onset of first deflection of QRS of ECG

Interventricular septal amplitude (IVSA)
Draw horizontal line between most posterior points of left ventricular side of septum during systole, then measure maximal vertical distance from this line to IVS just before septum begins to move posteriorly in systole.

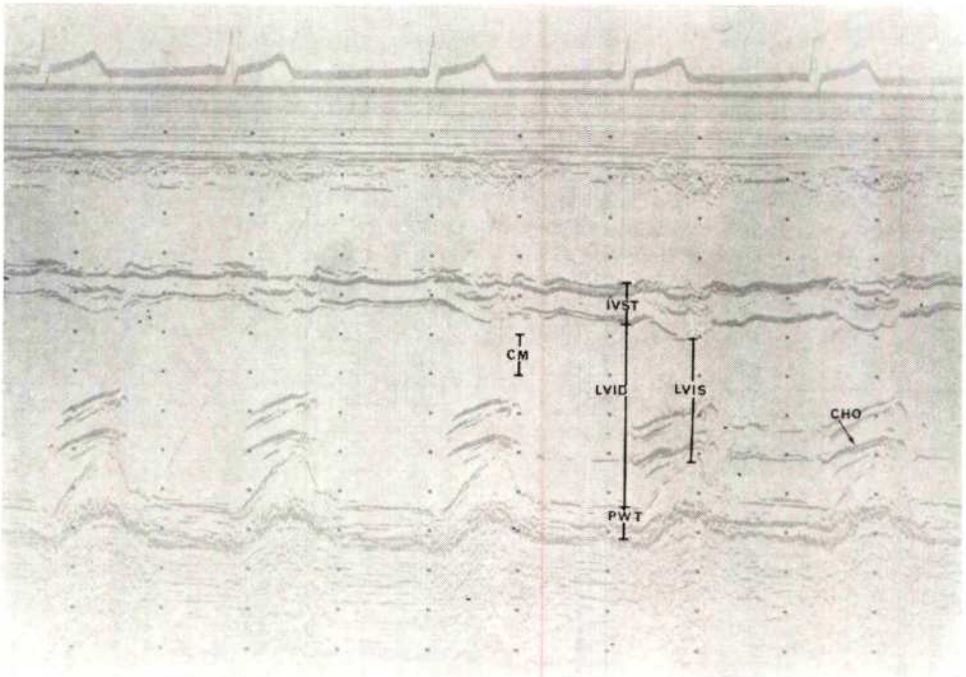

Fig. *Representative left ventricular echocardiogram. LVID, left ventricular diastolic dimension; LVIS, left ventricular systolic dimension; PWT, posterior wall thickness; CHO, chordae tendineae; IVST, intraventricular septal thickness.*

Table 3 . *F ratio of left ventricular measurements*

	LVIDd	*LVIDs*	*LVWT*	*LVWA*	*IVST*	*IVSA*
DF associated with error term	168	168	168	168	168	168
DF associated with weeks	3	3	3	3	3	3
F ratio associated with weeks	0·015	0·000	1·737	2·361	0·024	0·410
DF associated with observers	2	2	2	2	2	2
F ratio associated with observers	0·039	0·282	0·430	2·255	0·048	0·045
DF associated with interaction between weeks and observers	6	6	6	6	6	6
F ratio associated with interaction between weeks and observers	0·172	0·266	0·739	0·191	0·609	0 395

DF, degree of freedom.

Results

A two-way analysis of variance with replication was used to assess the effect of both week-to-week and interobserver variation, and interaction between the two on the indices studied. This did not show any statistically significant variation though the week-to-week variation was consistently greater than the interobserver variation (Table 3).

Since the two-way analysis of variance did not show any statistically significant variation of measurements from week to week, between observers, or for interaction between weeks and observers, and in order to have an estimate of the error attached to each measurement, we pooled all measurements by the three observers for each subject for four weeks to calculate the mean, standard deviation, and coefficient of variation as shown in Table 4. We chose to use the mean coefficient of variation for this estimate because, unlike the standard deviation, it took into account the magnitude of measurements (Table 5).

The 10 duplicated measurements unknown to the observers are shown in Table 6. The two rows of figures associated with each tracing are the two measurements by each observer. The maximum difference between two blind measurements of the same tracing was 0·3 cm for each of the observers. The mean absolute difference (taking the difference between two blind measurements as positive, the sum of all the differences divided by the number of observations) for each of the six left ventricular measurements by each observer was minimal (Table 6).

Cases 1 to 10 represent the normal volunteers and 11 to 15 the patients with valvular disorders (Table 4). The reason for including this latter group was not to compare them with the normal volunteers but simply to widen the range of ventricular measurements, thus providing a more representative mean coefficient of variation.

Discussion

Single plane M-mode echocardiography is now established as a valid method for measuring left ventricular wall and cavity dimensions.[3–6] Though undoubted limitations exist in its abilities to predict left ventricular function accurately, it appears to be of value in measuring serial changes within

Table 4 *Mean standard deviation (SD) and coefficient of variation (CV) of LV measurements in cm*

Case no.	*LVIDd*			*LVIDs*			*LVWT*			*LVWA*			*IVST*			*IVSA*		
	Mean	*SD*	*CV*	*Mean*	*SD*	*CV*	*Mean*	*SD*	*CV*	*Mean*	*SD*	*CV*	*Mean*	*SD*	*CV*	*Mean*	*SD*	*CV*
1	5 08	0·17	3·20	3·29	0·12	3·70	0·89	0·08	8·60	1·02	0·12	11·60	0·92	0·06	6·80	0·88	0·15	16·70
2	5·06	0·12	2·40	3·04	0·09	3·00	0·84	0·06	7·40	1·51	0·22	14·60	0·72	0·11	15·20	0·56	0·05	9·60
3	4·71	0·19	4·00	3·27	0·10	3·10	0·92	0·09	9·70	1·10	0·13	11·90	0·95	0·18	19·30	0·57	0·09	16·60
4	3·78	0·10	2·60	2·68	0·15	5·50	1·00	0·03	3·10	1·28	0·24	18·60	1·27	0·13	9·90	0·53	0·06	11·80
5	5·06	0·17	3·40	3·09	0·11	3·50	0·81	0·08	10·20	1·42	0·27	18·90	0·96	0·08	8·00	0·72	0·13	18·10
6	4·58	0·11	2·40	2·87	0·16	5·50	0·92	0·09	9·70	1·26	0·15	12·20	0·91	0·10	11·40	0·99	0·15	15·50
7	5·12	0·11	2·20	2·94	0·20	6·80	0·96	0·09	9·10	1·17	0·15	13·20	0·95	0·06	6·60	1·24	0·20	16·50
8	5·32	0·25	4·70	3·60	0·14	4·00	0·97	0·06	6·50	1·08	0·13	12·00	0·94	0·10	11·00	0·69	0·10	15·00
9	5·00	0·11	2·10	3·61	0·13	3·70	0·90	0·08	9·20	1·14	0·15	13·20	0·80	0·08	10·30	0·43	0·10	23·30
10	4·98	0·16	3·20	3·48	0·16	4·60	0·96	0·06	6·50	1·23	0·10	8·40	1·03	0·12	11·90	0·58	0·09	15·20
11	4·68	0·14	3·00	2·68	0·21	7·70	0·95	0·07	7·30	1·28	0·19	14·60	0·66	0·08	11·70	0·90	0·05	6·00
12	4·51	0·17	3·70	3·17	0·16	4·90	1·08	0·09	8·20	1·36	0·22	15·90	1·24	0·06	5·00	0·47	0·08	16·50
13	6·77	0·28	4·10	4·52	0·12	2·70	1·05	0·07	6·60	1·49	0·17	11·60	1·06	0·10	9·80	0·96	0·06	6·50
14	6·31	0·27	4·20	3·91	0·14	3·60	1·09	0·09	8·10	1·23	0·09	7·60	1·21	0·10	8·60	1·18	0·10	8·50
15	5·27	0·14	2·60	3·26	0·12	3·60	1·02	0·05	5·30	1·34	0·09	6·60	1·17	0·10	8·50	0·90	0·06	7·00

Table 5 *Mean coefficient of variation and 95 per cent confidence of left ventricular measurements in 15 subjects*

Index	*Mean coefficient of variation (%)*	*95 per cent confidence limit (2 × coefficient of variation)*
LVIDd	3·19	6·4
LVIDs	4·39	8·8
PLVWT	7·7	15·4
PLVWA	12·73	25·5
IVST	10·27	20·5
IVSA	13·58	27·2

an individual in response to different stimuli such as glyceryl trinitrate,[7–9] prazosin,[10] and propranolol.[11] None the less, in order to establish the true significance of changes in echo dimensions in response to interventions (particularly when the changes are small), it is important to establish the variability of this technique at different time intervals and between observers.

Earlier studies in echocardiographic diameter variability have shown differing results. Pombo *et al.*[12] noted differences of 3 ± 2·6 mm at end-diastole and 3·4 ± 3·4 at end-systole. They also showed that when two observers measured the same echocardiograms recorded by one individual there was less variation than when recorded by two individuals. Popp *et al.*[13] found that recording from one interspace reduced the variability of ventricular dimension measurements though Stefadouros and Canedo[14] still found significant variability within the same interspace and reduced this variability by standardising spatial orientation of the ultrasound beam. Sahn *et al.*[1] have shown significant interobserver and interlaboratory variation in measurement when examining the same echocardiogram and have emphasised the need for standardisation of measurements. Using their suggested guidelines we have shown no significant variation from week to week and by different observers. Furthermore the minimal intraobserver variation shown by the 10 blind duplicated tracings provides further evidence for consistency in echocardiographic measurements. Use of the pooled coefficient of variation has allowed us to define the extent of the variation and this is least with ventricular internal diameters and greatest with wall amplitudes (Table 5). Martin and Fieller[15] have recently studied ventricular dimension variability

Table 6 *Measurements of 10 blind duplicated tracings by three observers*

Observers tracing no.	*LVIDd*			*LVIDs*			*LVWT*			*LVWA*			*IVST*			*IVSA*		
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
1	4·8	4·9	4·9	3·3	3·4	3·3	0·9	0·9	0·9	1·0	1·0	0·9	0·9	1·0	0·9	0·7	0·8	0·8
	4·7	5·0	4·9	3·2	3·3	3·3	0·9	0·9	0·9	0·9	0·9	1·0	0·9	1·0	1·0	0·6	0·8	0·7
2	5·2	5·1	5·1	3·0	3·0	3·0	0·8	0·9	0·8	1·6	1·6	1·6	0·6	0·6	0·6	0·6	0·6	0·6
	5·2	5·1	5·0	3·0	3·0	3·0	0·8	0·9	0·9	1·7	1·6	1·5	0·7	0·7	0·7	0·6	0·7	0·6
3	4·6	4·5	4·5	3·2	3·2	3·2	0·8	1·0	1·0	1·0	1·1	1·0	1·1	1·1	0·9	0·6	0·6	0·7
	4·4	4·7	4·6	3·0	3·2	3·2	0·8	0·8	0·9	1·3	1·0	0·9	1·0	0·9	1·0	0·5	0·6	0·5
4	5·0	4·9	4·9	3·0	3·0	3·0	0·9	0·9	0·9	1·8	1·8	1·9	1·0	1·0	1·0	0·6	0·6	0·6
	4·9	4·9	5·0	3·0	2·7	3·1	1·0	0·9	0·9	1·8	1·8	1·6	0·9	1·0	0·9	0·5	0·6	0·6
5	4·7	4·5	4·6	2·8	2·9	2·8	0·8	0·9	0·8	1·3	1·3	1·3	0·9	0·9	1·0	1·2	1·1	1·1
	4·6	4·2	4·5	2·7	2·7	2·8	0·8	1·0	0·9	1·3	1·3	1·3	0·9	0·9	1·0	1·2	1·1	1·0
6	5·2	5·1	5·1	2·8	2·8	2·8	1·0	1·0	1·0	1·3	1·1	1·3	0·9	1·0	1·0	1·4	1·3	1·4
	5·4	5·0	5·0	2·7	2·6	2·7	1·0	1·0	1·0	1·3	1·1	1·3	1·0	0·9	1·0	1·4	1·3	1·4
7	5·2	5·1	5·1	3·7	3·7	3·7	1·0	1·0	1·0	1·2	1·0	1·1	0·9	1·1	1·1	0·7	0·6	0·7
	5·4	5·1	5·2	3·7	3·7	3·7	1·0	0·9	1·0	1·3	0·8	1·2	0·8	1·1	0·9	0·7	0·6	0·7
8	4·9	5·0	4·9	3·6	3·6	3·7	0·7	0·9	0·8	1·1	1·1	1·1	0·7	0·8	0·8	0·5	0·5	0·5
	5·1	5·0	4·9	3·6	3·6	3·7	0·8	0·9	0·9	1·2	1·0	0·9	0·7	0·8	0·8	0·5	0·5	0·5
9	5·2	5·1	5·1	3·5	3·5	3·5	1·0	0·9	0·9	1·3	1·2	1·2	1·1	1·2	1·2	0·6	0·6	0·7
	5·2	5·1	5·1	3·5	3·5	3·5	0·9	0·9	0·8	1·4	1·2	1·2	1·2	1·1	1·1	0·6	0·6	0·7
10	4·7	4·6	4·7	2·9	2·6	2·7	0·9	1·0	0·9	1·3	1·2	1·4	0·6	0·7	0·7	0·8	0·9	0·9
	4·8	4·7	4·8	3·1	2·5	2·7	0·9	1·0	0·9	1·3	1·3	1·3	0·6	0·7	0·6	0·8	0·8	0·9
Maximum difference	0·2	0·3	0·1	0·2	0·3	0·1	0·1	0·2	0·1	0·3	0·2	0·3	0·1	0·1	0·1	0·1	0·1	0·1
Mean absolute difference	0·12	0·08	0·07	0·07	0·08	0·02	0·03	0·04	0·04	0·08	0·06	0·1	0·06	0·04	0·08	0·03	0·02	0·04

at five minute intervals, hourly intervals, and weekly intervals. They found a progressive increase in variability with increasing time in intervals, with the coefficient of variation at one week being 5 per cent. Our coefficients of variation for diastolic dimension of 3·1 per cent and for systolic dimension of 4·4 per cent are of a similar magnitude despite the fact that we did not use any device for measuring the degree of lateral rotation.

In neither our study nor that by Martin and Feiller[15] were the echoes recorded at end expiration as suggested by Brenner and Waugh[16] who showed that phasic respiration had an effect on left ventricular dimensions. While it is true that this might have further reduced our variability, it is important to remember that some patients when instructed to suspend their respiration may breath hold thus producing an unintentional Valsalva which would further complicate data analysis and interpretation.

The use of computer programs for analysis of routine echocardiograms[17 18] has clear advantages over manual methods but such systems are expensive and confined to relatively few major centres. Our data confirm that accurate and reproducible measurements can be obtained using the methods described and can provide useful information on the degree of variability of left ventricular dimensions as measured by echocardiography.

Although we did not compare the variability caused by different individuals performing the echocardiograms, we feel that this would certainly have increased the variability, and the observations of Pombo *et al.*[12] support this. We also believe that the careful documentation of interspace and distance from sternum of the probe have further reduced the variability. While we did not accurately measure the angle of the patient, approximately the same position was used in each patient during repeat studies. We feel that this would be acceptable in serial studies and that unless small changes were being expected the device of Martin and Fieller[15] for measuring degree of lateral rotation is not mandatory.

In conclusion, we recommend that in sequential follow-up of patients using M-mode echocardiography one individual should perform all the recordings and that the patient and transducer position should be carefully documented. Furthermore it is essential to use uniform guidelines for measurements such as those suggested by the American Society of Echocardiography. Our findings support the recommendations made recently on the use of M-mode echocardiography in clinical pharmacology.[19]

References

1 Sahn DJ, DeMaria A, Kisslo J, Weyman A. The committee on M-mode standardization of the American Society of Echocardiography. Recommendations regarding quantification in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; **58:** 1072–83.

2 Henry WL, Clark CE, Epstein SE. Asymmetric septal hypertrophy. Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation* 1973; **47:** 225–33.

3 Feigenbaum H, Popp RL, Chip JN, Haine CL. Left ventricular wall thickness measured by ultrasound. *Arch Intern Med* 1968; **121:** 391–5.

4 Chapelle M, Mensch B. Etude des variations du diamètre ventriculare gauche chez l'homme par échocardiographie transthoracique. *Arch Mal Coeur* 1969; **62:** 1505–17.

5 Feigenbaum H. Wolfe SB, Popp RL, Haine CL, Dodge HT. Correlation of ultrasound and angiocardiography in measuring left ventricular diastolic volume (abstract). *Am J Cardiol* 1969; **23:** 111.

6 Troy BL, Pombo J, Rackley CL. Measurement of left ventricular wall thickness and mass by echocardiography. *Circulation* 1972; **45:** 602–11.

7 Redwood DR, Henry WL, Epstein SE. Evaluation of the ability of echocardiography to measure acute alterations in left ventricular volume. *Circulation* 1974; **50:** 901–4.

8 Burggraf GW, Parker JO. Left ventricular volume changes after amyl nitrite and nitroglycerin in man as measured by ultrasound. *Circulation* 1974; **49:** 136–43.

9 Hardarson J, Wright KE. Effect of sublingual nitroglycerin on cardiac performance in patients with coronary artery disease and non-dyskinetic left ventricular contraction. *Br Heart J* 1976; **38:** 1272–7.

10 Awan NA, Miller RR, Mason DT. Comparison of effects of nitroprusside and prazosin on left ventricular function and the peripheral circulation in chronic refractory congestive heart failure. *Circulation* 1978; **57:** 152–9.

11 Frishman W, Smithen C, Befler B, Kligfield P, Killip T. Noninvasive assessment of clinical response to oral propranolol therapy. *Am J Cardiol* 1975; **35:** 635–44.

12 Pombo JF, Troy BL, Russell RO Jr. Left ventricular volumes and ejection fraction by echocardiography. *Circulation* 1971; **43:** 480–90.

13 Popp RL, Filly K, Brown OR, Harrison DC. Effect of transducer placement on echocardiographic measurement of left ventricular dimensions. *Am J Cardiol* 1975; **35:** 337–40.

14 Stefadouros MA, Canedo MI. Reproducibility of echocardiographic estimates of left ventricular dimensions. *Br Heart J* 1977; **39:** 390–8.

15 Martin MA, Fieller NRJ. Echocardiography in cardiovascular drug assessment. *Br Heart J* 1979; **41:** 536–43.

16 Brenner JI, Waugh RA. Effect of phasic respiration on left ventricular dimension and performance in a normal population. An echocardiographic study *Circulation* 1978; **57**: 122–7.

17 Gibson DG, Brown D. Measurement of instantaneous left ventricular dimension and filling rate in man, using echocardiography. *Br Heart J* 1973; **35**: 1141–9.

18 Griffith JM, Henry WL. Video scanner—analog computer system for semiautomatic analysis of routine echocardiograms. *Am J Cardiol* 1973; **32**: 961–4.

19 Gibson DG. Use of m-mode echocardiography in clinical pharmacology. *Br J Clin Pharmacol* 1979; **7**: 443–9.

Requests for reprints to Dr F G Dunn, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, Louisiana 70121, USA.

Br Heart J 1980; **44:** 290–6

Captopril in clinical hypertension

Changes in components of renin-angiotensin system and in body composition in relation to fall in blood pressure with a note on measurement of angiotensin II during converting enzyme inhibition

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SUMMARY The effect of the converting enzyme inhibitor captopril on arterial pressure, the components of the renin-angiotensin-aldosterone system, and body sodium and potassium content was studied in eight hypertensive patients with renal artery stenosis and, in conjunction with diuretics, in seven patients with hypertension unresponsive to previous treatment. Two hours after the first dose, captopril caused significant falls in systolic and diastolic pressures, plasma angiotensin II, and aldosterone, with converse increases in angiotensin I and both active and total renin; the initial fall in diastolic pressure was significantly related to the drop in plasma angiotensin II. The biochemical changes were sustained during prolonged treatment, even when diuretics were added.

One untreated patient with renal artery occlusion had severe secondary aldosterone excess, was sodium and potassium depleted, and severely hyponatraemic and hypokalaemic; captopril restored blood pressure, plasma electrolyte concentrations, and exchangeable sodium and total body potassium to normal. In one man with renal artery stenosis and overall renal impairment captopril led to sodium retention, and blood pressure did not fall until a diuretic was added. In the remaining patients with renal artery stenosis, pretreatment renin, angio tensin II, and aldosterone concentrations were either normal or only modestly raised, and plasma electrolyte concentrations and body content of sodium and potassium were normal. Captopril alone controlled arterial pressure in all, three cases showing a gradual fall of pressure over the first six weeks of treatment; no significant changes in exchangeable sodium or total body potassium were seen.

The group of patients with previously intractable hypertension were all controlled with a combination of captopril and diuretic.

Clinical accounts of the use of captopril (Squibb SQ 14 225), an inhibitor of the enzyme responsible for the conversion of angiotensin I to angiotensin II, have hitherto concentrated largely on the hypotensive action, the suppression of aldosterone, and the relation to pretreatment plasma renin levels.[1–5] There have been few reports of alterations in circulating concentrations of angiotensin I and II during treatment.[6–8] Lowering of plasma angiotensin II concentration is probably a major, though not the only, mechanism of the hypotensive action of captopril.[1] Evaluation of the body content of sodium or potassium before and during captopril treatment is also of interest, because the pressor effect of angiotensin II is directly related to the body content of sodium; moreover, body potassium might be expected to increase and sodium to decrease with captopril treatment, as angiotensin II, and hence aldosterone, falls.

We give here a detailed analysis of measurements of the individual components of the renin-angiotensin aldosterone system, and of sodium and potassium status, in relation to the fall in arterial pressure

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Table 1 *Effect of captopril alone on blood pressure, plasma angiotensin II, and aldosterone, and on plasma and body compositions of potassium and sodium in eight patients with renal artery lesions (mean ± SEM)*

	Before captopril	*Two hours after first dose of captopril*	*After six days on captopril*	*After six weeks on captopril*
Blood pressure (mmHg)	183/115 ± 10/5	152/97 ± 12/8 (p < 0·01)	159/95 ± 8/6 (p < 0·02)	149/89 ± 8/7 (p < 0·02)
Plasma angiotensin II (pg/ml)	104·9 ± 87·0	20·1 ± 13·2 (p < 0·02)	22·6 ± 15·6 (p < 0·02)	13·5 ± 7·7 (p < 0·02)
Plasma aldosterone (ng/100 ml)	19·6 ± 7·8	13·9 ± 6·5 (p < 0·05)	10·4 ± 1·5 (NS)	8·1 ± 1·3 (NS)
Total exchangeable sodium (mmol)	2458 ± 289	—	—	2493 ± 275 (NS)
Total body potassium (mmol)	2920 ± 331	—	—	2842 ± 355 (NS)
Plasma sodium (mmol/l)	137·6 ± 2·0	—	—	137·9 ± 1·0 (NS)
Plasma potassium (mmol/l)	3·8 ± 0·3	—	—	4·4 ± 0·2 (p < 0·05)

during oral captopril treatment. Two types of patients were studied; the first group had renal artery stenosis (Table 1), while all of the second group had been resistant to previous antihypertensive treatment (Table 2).

A brief account of this work was presented to the International Society of Hypertension, Göteborg, 1979.[9]

Methods

Fourteen patients were investigated. Plasma concentrations of active (normal range 10 to 50 uU/ml) and total (normal 60 to 200 uU/ml) renin, angiotensin II (5 to 33 pmol/l; 5 to 35 pg/ml), and aldosterone (< 499 pmol/l; < 18 ng/dl), and blood concentrations of angiotensin I (8 to 73 pmol/l; 10 to 90 pg/ml) were measured in peripheral venous blood by methods described previously.[8]

CORRECTION FOR ANGIOTENSIN I CROSS-REACTION

The angiotensin II antiserum used in these studies has a low cross-reaction (less than 1·0%) with angiotensin I; therefore under normal circumstances this does not cause technical difficulty with angiotensin II assay. When converting enzyme is inhibited, however, high concentrations of renin and hence angiotensin I build up in the circulation, while plasma angiotensin II falls to very low levels; moreover, further generation of angiotensin I can occur during the processing of plasma extracts. Thus, falsely high values for plasma angiotensin II can be obtained with immunoassay unless technical precautions are taken, particularly in patients with raised endogenous renin levels. In earlier studies, this was corrected by prior chromatography[10]; in the present work, a simpler method was used as follows. Increasing quantities of exogenous angiotensin I (ileu 5; Schwarz/Mann) (from 1·2 to 7·2 ng) were added to a pooled plasma extract and the apparent increase in angiotensin II was measured by radioimmunoassay. The results are plotted in Fig 1 and show a linear relation between the amount of angiotensin I added and the apparent increase in angiotensin II. Subsequently, in all plasma samples after extraction, both angiotensin I and angiotensin II were estimated. Using Fig. 1, the appropriate correction factor was calculated, taking into account the cross-reaction caused by angiotensin I. This was then applied in determining the circulating angiotensin II concentration.

Table 2 *Effect of captopril and diuretics in a group of seven patients with severe treatment-resistant hypertension (mean ± SEM)*

	Before captopril	*On captopril alone*	*On captopril plus diuretics (3 to 26 days)*	*On captopril plus diuretics (3 months)*
Blood pressure (mmHg)	215/116 ± 11/8	199/114 ± 15/8 (NS)	153/93 ± 10/6 (p < 0·05)	140/90 ± 8/2 (p < 0·05)
Plasma angiotensin II (pg/ml)	39·8 ± 15·9	11·9 ± 2·7 (p < 0·05)	7·3 ± 2·4 (p < 0·05)	—
Plasma aldosterone (ng/100 ml)	13·0 ± 2·6	7·9 ± 1·4 (NS)	10·4 ± 1·4 (NS)	—

Patients

All patients took a constant diet which was the same for each subject on each admission to the metabolic ward; sodium and potassium content varied between individuals from 85 to 155 and 44 to 90 mmol per day, respectively.

Eight patients (Table 1) had renal ischaemia. It is our practice to take the findings at ureteric catheterisation as the most reliable criteria of unilateral renal ischaemia, the essential features being reduced urine flow, creatinine, and para-aminohippurate (PAH) clearances and urinary sodium concentration, with increased urinary creatinine and PAH concentrations, on the affected side. Increased ipsilateral renal vein renin and angiotensin II concentrations are often corroborative, but less specific features.[11–14] Seven patients had the typical radiological and ureteric catheterisation findings of unilateral renal artery stenosis, together with appropriate lateralising features on renal vein sampling for renin and angiotensin.[13 14] One patient, previously in the malignant phase, was presumed to have consequent and predominantly unilateral intrarenal arterial lesions, having normal renal arteriograms, but evidence of unilateral renal ischaemia on both renal vein sampling and ureteric catheterisation. None of the patients with renal ischaemia had received any treatment other than bethanidine for four weeks before study; bethanidine was stopped 12 or more hours before the initial dose of captopril.

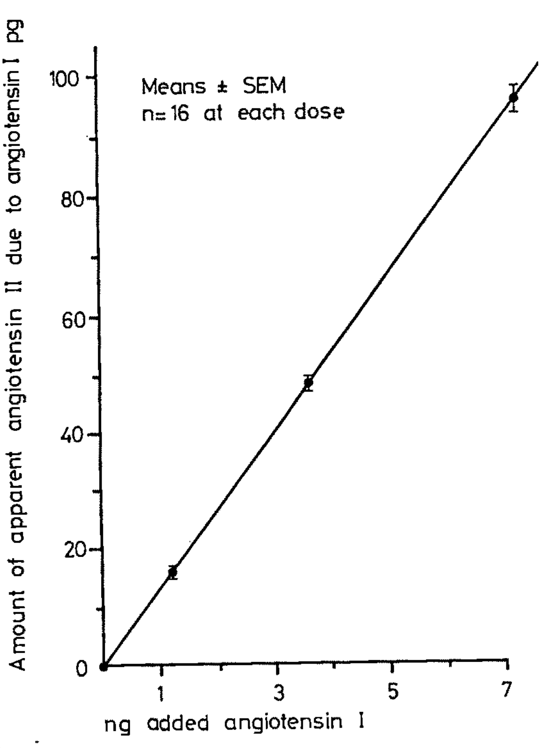

Fig. 1 *Apparent increase in angiotensin II caused by the cross-reaction of the antiserum with increasing amounts of angiotensin I added to a pooled plasma extract.*
Each point is the mean ±SEM of 16 separate estimates at each dose of added exogenous angiotensin I.

A further six patients (Table 2) had severe hypertension unresponsive to a combination of diuretic and beta-adrenoceptor blocker together with either a vasodilator or a post-synaptic alpha-adrenoceptor blocking agent. All were on this combination immediately before captopril treatment. One patient in the renal artery stenosis series was added to this group as his blood pressure before captopril had been unresponsive to treatment.

Blood samples were taken, after overnight recumbency and fasting, at 0930 hours and 1000 hours. The initial dose of captopril (25 mg in 10 cases, 6·25 mg in three cases) was then given and further samples were taken after two hours and six hours, respectively. The patients remained recumbent throughout and fasted until the two hour sample had been taken. The maximum captopril dosage used long term was 450 mg per day. In the patients with renal artery stenosis, the values given for the various components of the renin-angiotensin-aldosterone system during prolonged treatment are the means obtained in samples taken at 1000, 1200, and 1600 hours, 150 mg captopril having been given at 2200 hours on the previous evening, and again immediately after the 1000 hours sample. In the patients with drug-resistant hypertension the values are those obtained at 1000 hours, 12 hours after the previous dose of captopril and diuretic.

Exchangeable sodium (NaE),[15] exchangeable potassium (KE),[15] and total body potassium (TBK)[16] were measured by isotope dilution; in one man total body sodium (TBNa)[17] was measured by activation analysis. The relation between NaE and plasma angiotensin II in patients before and during treatment was expressed in comparison with data previously obtained in normotensive subjects.[18 19]

Throughout the study blood pressures were taken after at least 10 minutes rest. A routine clinical sphygmomanometer was used; phase V was taken as diastolic. Mean blood pressure was taken as diastolic plus one-third of pulse pressure.

Non-parametric statistical tests (Wilcoxon signed rank and Spearman rank correlation) were used as the data were not distributed normally.

Results

PATIENTS WITH RENAL ARTERY STENOSIS (Table 1)

One patient has been reported in detail elsewhere.[8] This woman had unilateral renal artery occlusion and developed classical features of the hyponatraemic hypertensive syndrome.[8 20–22] She was initially severely sodium and potassium depleted, with hyponatraemia and hypokalaemia and raised plasma concentrations of renin, angiotensin II, and aldosterone. Plasma angiotensin II fell steeply after the initial dose of captopril. Because the maintenance of arterial pressure is heavily dependent on plasma angiotensin II in sodium depletion, the initial fall of blood pressure was pronounced. With continued captopril treatment, sodium was steadily retained, the cumulative balance increasing by 598 mmol over eight days. In the same period 226 mmol potassium were retained and the plasma sodium and potassium concentrations reverted to normal. Blood pressure stabilised at a higher level as the electrolyte abnormalities were corrected and became similar to that seen after subsequent unilateral nephrectomy.

One patient with renal artery stenosis had impaired overall renal function (creatinine clearance 30 ml/min). On captopril alone TBNa rose by 157 mmol over two weeks and blood pressure remained high (190/120 mmHg) despite the drop in plasma angiotensin II. Blood pressure fell to 130/90 mmHg, and remained well controlled under outpatient conditions, when 80 mg frusemide daily was added.

The remaining patients in this group had good overall renal function, normal or only modestly raised plasma concentrations of renin, angiotensin II, and aldosterone, normal plasma electrolytes and body sodium and potassium. Captopril induced an initial modest fall in arterial pressure in parallel with the fall in plasma angiotensin II; a further distinct reduction in blood pressure was seen over six weeks with continued treatment in three patients. In this whole group, throughout the period of observation on captopril, plasma angiotensin II and aldosterone remained suppressed, while active and total renin, and angiotensin I, were raised. Plasma sodium was unchanged, while mean plasma potassium rose marginally; frank hyperkalaemia was not encountered in any case. There was no appreciable change in mean NaE or TBK.

PATIENTS WITH INTRACTABLE HYPERTENSION (Table 2)

Captopril alone did not significantly reduce arterial pressure compared with the previous regimens, though mean plasma angiotensin II fell significantly. When either hydrochlorothiazide (50 mg twice daily) or frusemide (from 40 to 1500 mg/day) was given in addition to captopril, arterial pressure was clearly lower. During continued treatment with combined diuretic and captopril, blood pressure continued well controlled and plasma angiotensin II remained suppressed. Plasma aldosterone was not significantly altered by adding diuretic to captopril. Treatment has now continued for up to 15 months in this group with no loss of control.

RESUME OF BIOCHEMICAL CHANGES IN RELATION TO FALLS IN ARTERIAL PRESSURE

Two hours after the initial dose of captopril, there were highly significant falls in systolic and diastolic pressure, plasma angiotensin II, and aldosterone concentrations, and increases in the plasma concentrations of active and total renin and blood concentrations of angiotensin I (Table 3). There was a highly significant correlation between the fall in plasma angiotensin II and fall in diastolic blood pressure ($r_s = 0{\cdot}71$; $p < 0{\cdot}01$; Fig. 2) and, less closely, between the fall in plasma angiotensin II and mean blood pressure ($r_s = 0{\cdot}48$; $p < 0{\cdot}05$).

Seven patients in the series were studied after at least six weeks of treatment with captopril 450 mg/day; five were on captopril alone and two were receiving diuretics also (Table 4). While plasma concentrations of active renin, total renin, and blood levels of angiotensin I continued to be significantly raised, plasma angiotensin II remained suppressed, as did plasma aldosterone.

SIDE EFFECTS

One patient with renal artery occlusion and sodium depletion became hypotensive after the initial dose

Table 3 *Effect at two hours of the initial dose of captopril on blood pressure and circulating concentrations of active renin, total renin, angiotensin I, angiotensin II, and aldosterone in 14 hypertensive patients (mean ± SEM)*

	Before captopril	*Two hours after captopril*
Blood pressure (mmHg)	195/118 ± 10/5	166/100 ± 10/6 ($p < 0{\cdot}01$)
Plasma active renin (uU/ml)	202·9 ± 95·2	449·1 ± 120·1 ($p < 0{\cdot}01$)
Plasma total renin (uU/ml)	448·4 ± 217·8	695·7 ± 201·9 ($p < 0{\cdot}01$)
Plasma angiotensin I (pg/ml)	98·3 ± 61·9	257·0 ± 93·7 ($p < 0{\cdot}01$)
Plasma angiotensin II (pg/ml)	78·6 ± 49·6	23·1 ± 11·5 ($p < 0{\cdot}01$)
Plasma aldosterone (ng/100 ml)	17·3 ± 4·6	11·5 ± 3·8 ($p < 0{\cdot}01$)

of 25 mg. Our recommendations in these circumstances have been reported previously.[1, 8] In addition, the controlled intravenous infusion of angiotensin II (Hypertensin, Ciba) might usefully be considered as a means of preventing hypotension and regulating arterial pressure accurately if captopril is given to a sodium-depleted patient (as may be necessary for example, if earlier diuretic treatment has been employed for cardiac failure). Sodium can then be more safely replaced as the blood pressure is lowered, and with continued captopril treatment angiotensin II administration becomes unnecessary.[23]

Two patients developed symptomatic sinus tachycardia (up to 160 beats/min) on standing, one while on captopril alone and one after hydrochlorothiazide was added.

Two patients had disturbance of taste which in both instances resolved over a period of four weeks with continued treatment.

Serum urea and creatinine tended to rise when frusemide was added, particularly in patients with renal impairment; these should therefore be monitored closely.

Discussion

We have previously reported that during treatment with converting enzyme inhibitors high concentrations of angiotensin I may accumulate in plasma to such an extent that cross-reaction of angiotensin I with antibodies to angiotensin II may give falsely high values for plasma angiotensin II.[1, 8–10, 17, 23, 24] In the light of this we have developed a method of estimating the extent of the interference so that the data can be more accurately interpreted.

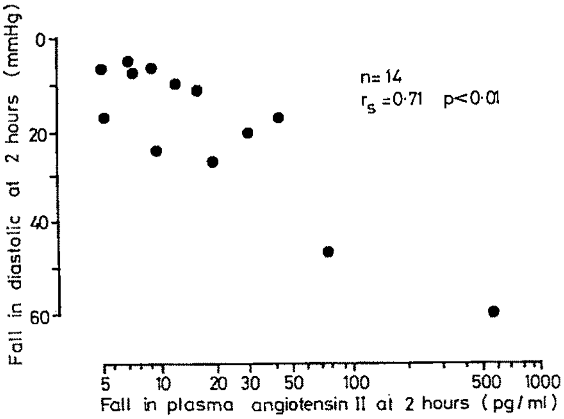

Fig. 2 *Relation between falls in diastolic pressure and angiotensin II two hours after initial dose of captopril. Not plotted, but included in the calculation, are data from one patient who had no change in angiotensin II and a fall of 8 mmHg in diastolic pressure.*

Table 4 *Long-term effects of captopril in circulating concentrations of active renin, total renin, angiotensin I, angiotensin II, and aldosterone in seven patients, all of whom had been on drugs for at least six weeks (mean ±SEM)*

	Before captopril	*After captopril*
Plasma active renin (uU/ml)	74·6 ±13·8	794·3 ±22·0 ($p < 0·05$)
Plasma total renin (uU/ml)	153·0 ±21·8	1008·0 ±260·3 ($p < 0·05$)
Plasma angiotensin I (pg/ml)	12·3 ±14·2	193·7 ±37·1 ($p < 0·05$)
Plasma angiotensin II (pg/ml)	19·9 ±3·6	4·8 ±0·8 ($p < 0·05$)
Plasma aldosterone (ng/100 ml)	14·0 ±2·7	8·7 ±1·3 ($p < 0·05$)

We have seen that prolonged treatment with oral captopril leads to clear and sustained falls in plasma angiotensin II and aldosterone, despite distinct increases in circulating active renin and angiotensin I concentrations. A similar pattern of changes was seen by Johnston and colleagues[7] when captopril was given to patients with essential hypertension, except that in their study captopril given alone did not cause an increase in blood angiotensin I. A significant correlation was seen in the present series between the initial fall in plasma angiotensin II and the concurrent drop in arterial pressure. Several lines of evidence indicate, however, that components additional to the reduction of plasma angiotensin II are involved in the hypotensive action of captopril. Experimental studies in this department on dogs showed that changes in plasma angiotensin II alone were insufficient to account for the acute changes in blood pressure.[25] Moreover, captopril has been found to lower blood pressure both in anephric rats and man.[26, 27]

In addition to the initial fall in blood pressure, in three patients with renal artery stenosis in the present series (Table 1), a further reduction in pressure was seen during prolonged treatment. A similar slow fall in pressure has been noted in other series,[3] and is also a feature of prolonged administration of saralasin or converting enzyme inhibitors to rats with one-clip, two kidney renal hypertension.[28, 29] This late effect is compatible with, but does not establish, antagonism of a slow pressor action of angiotensin II[1]; on present evidence it could equally represent some other component of captopril action.

There is a close interdependence between sodium status and angiotensin II in blood pressure maintenance[24] and therefore an important determinant of the pressor effect of a given plasma concentration of angiotensin II is NaE (or TBNa). In previous studies, hypertension in patients with chronic renal failure or the malignant phase was shown to be associated with a disproprotionate increase in plasma angiotensin II in relation to NaE.[18,19] Blood pressure came down when this disproportion was corrected by lowering either plasma angiotensin II or NaE. In the present series a similar disproportion was seen, despite a low NaE, in one patient with the hyponatraemic hypertensive syndrome; the angiotensin II:NaE relation was corrected, and blood pressure fell, with captopril.[8] In another patient, with renal impairment, sodium retention developed on captopril, and, despite the fall in plasma angiotensin II, blood pressure remained high until a natriuretic agent was added.

In the remaining patients with renal artery stenosis, the relation between angiotensin II and NaE was normal before treatment, which lowered angiotensin II and blood pressure without detectably changing NaE. Brunner and colleagues[4] reported a fall in blood pressure on giving captopril to hypertensive patients with chronic renal failure, and interpreted this as confirming earlier descriptions[18,19] of a disproportionate rise of angiotensin II in relation to NaE in these circumstances. While this may be so, neither angiotensin II nor NaE was measured in their study.[4] As seen here, a similar outcome could be the result of a fall in plasma angiotensin II without a change in NaE, in circumstances where the initial relation between the two measurements was normal.

It is to be expected that the addition of natriuretic treatment to captopril should be powerfully antihypertensive.[1] Sodium is lost from the body and the compensatory increases in plasma angiotensin II and aldosterone are prevented. Though failures have been reported with this combination,[1] it was consistently effective in the present series, despite several patients having been resistant to previous drugs in various combinations and in optimal dose. Contrary to earlier reports,[1] however, we did find tachycardia, especially on orthostasis, to be troublesome, and several patients developed increases in plasma creatinine, when captopril was given with a diuretic.[1] Careful clinical and biochemical surveillance is therefore necessary in these circumstances.

Although captopril is undoubtedly effective,[1,23] side effects are not negligible, and a final evaluation of its role in the treatment of hypertension remains for the future.

References

1 Atkinson AB, Robertson JIS. Captopril in the treatment of clinical hypertension and cardiac failure. *Lancet* 1979; **ii:** 836–9.

2 Brunner HR, Gavras H, Waeber B, *et al.* Oral angiotensin-converting enzyme inhibitor in long-term treatment of hypertensive patients. *Ann Intern Med* 1979; **90:** 19–23.

3 Atlas SA, Case DB, Sealey JE, Laragh JH, McKinstry DK. Interruption of the renin-angiotensin system in hypertensive patients by captopril induces sustained reduction in aldosterone secretion, potassium retention, and natriuresis. *Hypertension* 1979; **1:** 274–80.

4 Brunner HR, Waeber B, Wauters JP, Turini G, McKinstry D, Gavras H. Inappropriate renin secretion unmasked by captopril (SQ 14 225) in hypertension of chronic renal failure. *Lancet* 1978; **ii:** 704–7.

5 Bravo EL, Tarazi RC. Converting enzyme inhibition with an orally active compound in hypertensive man. *Hypertension* 1979; **1:** 39–46.

6 Amery A, Fagard R, Lijnen P, Reybrouck T. Comparison between captopril and saralasin in hypertensive patients. Abstracts, 6th Scientific Meeting of International Society of Hypertension, Göteborg, 1979: p. 119.

7 Johnston CI, Millar JA, McGrath BP, Matthews PG. Long-term effects of captopril (SQ 14 225) on blood pressure and hormone levels in essential hypertension. *Lancet* 1979; **ii:** 493–6.

8 Atkinson AB, Brown JJ, Davies DL *et al.* Hyponatraemic hypertensive syndrome with renal artery occlusion corrected by captopril. *Lancet* 1979; **ii:** 606–8.

9 Atkinson AB, Brown JJ, Fraser R, *et al.* Captopril in hypertension with renal artery stenosis and in intractable hypertension; acute and chronic changes in circulating concentrations of renin, angiotensins I and II and aldosterone, and in body composition. *Clin Sci* 1979; **57:** 139S–43S.

10 Morton JJ, Casals-Stenzel J, Lever AF, Millar JA, Riegger AJG, Tree M. Inhibitors of the renin-angiotensin system in experimental hypertension, with a note on the measurement of angiotensin I, II and III during infusion of converting-enzyme inhibitor. *Br J Clin Pharmacol* 1979; **7,** suppl 2: S233–S41.

11 Brown JJ, Owen K, Peart WS, Robertson JIS, Sutton D. The diagnosis and treatment of renal-artery stenosis. *Br Med J* 1960; **ii:** 327–38.

12 Brown JJ, Lever AF, Robertson JIS. Renal hypertension: aetiology, diagnosis and treatment. In: Black DAK, Jones NF, eds. *Renal disease.* 4th ed. Oxford: Blackwell, 1979: 731–65.

13 Millar JA, Leckie BJ, Semple PF, Morton JJ, Sonkodi S, Robertson JIS. Active and inactive renin in human plasma. *Circ Res* 1978; **43,** suppl I: 120–7.

14 Semple PF, Cumming AMM, Millar JA. Angiotensins I and II in renal vein blood. *Kidney Int* 1979; **15:** 276–82.

15 Davies DL, Robertson JWK. Simultaneous measurement of total exchangeable potassium and sodium using ^{43}K and ^{24}Na. *Metabolism* 1973; **22:** 133–7.

16 Boddy K, King PC, Tothill P, Strong JA. Measurement of total body potassium with a shadow shield

whole-body counter: calibration and errors. *Phys Med Biol* 1971; **16:** 275–82.

17 Boddy K, Brown JJ, Davies DL, *et al.* Concurrent estimation of total body and exchangeable body sodium in hypertension. *Clin Sci Mol Med* 1978; **54:** 187–91.

18 Davies DL, Schalekamp MA, Beevers DG, *et al.* Abnormal relation between exchangeable sodium and the renin-angiotensin system in malignant hypertension and in hypertension with chronic renal failure. *Lancet* 1973; **i:** 683–7.

19 Schalekamp MA, Beevers DG, Briggs JD, *et al.* Hypertension in chronic renal failure: an abnormal relation between sodium and the renin-angiotensin system. *Am J Med* 1973; **55:** 379–90.

20 Bauer H, Forbes GL. Unilateral renal artery obstruction associated with malignant nephrosclerosis confined to the opposite kidney. *Am Heart J* 1952; **44:** 634–8.

21 Brown JJ, Davies DL, Lever AF, Robertson JIS. Renin and angiotensin. A survey of some aspects. *Postgrad Med J* 1966; **42:** 153–76.

22 Barraclough MA. Sodium and water depletion with acute malignant hypertension. *Am J Med* 1966; **40:** 265–72.

23 Atkinson AB, Brown JJ, Fraser R, *et al.* Antagonists and inhibitors of the renin-angiotensin-aldosterone system in the treatment of hypertension. In: Robertson JIS, Pickering GW, eds. *The therapeutics of hypertension.* London: Academic Press, 1980: 29–61.

24 Atkinson AB, Brown JJ, Davies DL, *et al.* Captopril, angiotensin II, and sodium in blood-pressure regulation (letter). *Lancet* 1979; **i:** 1140.

25 Tree M, Morton JJ, Captopril lowers blood pressure by an additional mechanism independent of angiotensin II (abstract). *Clin Sci* 1980; **58:** 2P.

26 Marks ES, Bing RF, Thurston H, Swales JD. Vasodepressor property of the converting enzyme inhibitor captopril (SQ 14 225): the role of factors other than renin-angiotensin blockade in the rat. *Clin Sci* 1980; **58:** 1–6.

27 Man in't Veld AJ, Schicht IM, Derkx FHM, DeBruyn JHB, Schalekamp MADH. Effects of an angiotensin-converting enzyme inhibitor (captopril) on blood pressure in anephric subjects. *Br Med J* 1980; **i:** 288–90.

28 Riegger AJG, Lever AF, Millar JA, Morton JJ, Slack B. Correction of renal hypertension in the rat by prolonged infusion of angiotensin inhibitors. *Lancet* 1977; **ii:** 1317–9.

29 Atkinson AB, Brown JJ, Fraser R, *et al.* Angiotensin II and renal hypertension in dog, rat and man: effect of converting enzyme inhibition. *Clinical and Experimental Hypertension* 1980; **2:** 499–524.

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Changes in ventricular size and plasma renin activity after cardiac surgery in children*†

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SUMMARY Plasma renin activity and one-dimensional echocardiographic measurements of the left atrium and left ventricle as well as function indices were studied repeatedly in 20 children with various cardiopathies (ages: 9 months to 15 years) before and after corrective surgery. Nine children had tetralogy of Fallot, four had pulmonary stenosis, four had rheumatic heart disease, two had ventricular septal defect, and one had atrial septal defect.

Plasma renin activity was normal preoperatively, but increased significantly immediately after surgery, was still significantly higher on the 12th postoperative day and returned to normal six to eight weeks after surgery. Patients with tetralogy of Fallot and pulmonary stenosis had higher plasma renin activity values than the others.

There was a positive correlation between plasma renin activity and postoperative percentage change of the left ventricular dimension. In patients with tetralogy of Fallot and pulmonary stenosis, this meant that plasma renin activity became normal when the preoperatively small left ventricle reached its normal dimension. This adjustment occurred slowly over a period of two months. In rheumatic heart disease and left-to-right shunt lesions, plasma renin activities became normal when the preoperatively dilated left ventricle decreased in size towards normal values; the plasma renin activities of these patients had reached normal levels by the fifth postoperative day.

The renin secretion is modulated by various factors: of these, ventricular size and pulmonary venous return seem to be of importance.

In a previous study on renal function in children on the second day after cardiac surgery,[1] determinations of plasma renin activity (unpublished data) demonstrated a rise in most patients. This rise was particularly important in several cases of tetralogy of Fallot and pulmonary stenosis, and was not related to changes in renal function. An increase in plasma renin activity might be caused by different factors linked to haemodynamic changes induced by cardiac surgery. A prospective study was therefore undertaken in children who were operated on for different types of cardiac lesions, comparing plasma renin activity values and left atrial and left ventricular dimensions as well as cardiac function indices obtained before and after operation by one-dimensional echocardiography.

Subjects and methods

A randomly selected group of 20 children was studied. Table 1 summarises their clinical data. All patients underwent open heart surgery with cardiopulmonary bypass. Their postoperative fluid management consisted of glucose 5 per cent given at a rate of 750 ml/m^2 per 24 h with 2 mmol/kg per 24 h of NaCl and of KCl, respectively. The fluid volume was progressively increased after the first postoperative day. Cardiac failure was treated in most of the patients with digoxin and diuretics (frusemide, thiazide, and spironolactone) for up to two months after operation. Whenever necessary, cardiotonic drugs were added during the first two days. Blood pressure was measured directly through an arterial catheter (mean BP) for approximately 48 hours and thereafter by auscultation. Serum electrolyte levels (Na, K, Cl, CO_2) and serum and urine creatinine were determined daily during the first six postoperative days and weekly thereafter.

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On each patient, serial plasma renin activity determinations and echocardiograms were performed according to the following schedule:

I: preoperatively
II: *2nd* postoperative day
III: *5th* postoperative day
IV: *12th* postoperative day
V: *4 to 8 weeks* postoperatively.

Blood samples were drawn, usually in the morning, after the patients had remained in the supine position for at least two hours. The samples were collected in chilled tubes containing EDTA, and were then centrifuged at 4°C. The plasma renin activity was determined by radioimmunoassay of angiotensin I generated during one hour of incubation,[2] assay being adapted to the antibody trapping method of Poulsen.[3]

ECHOCARDIOGRAPHIC TECHNIQUE

The echocardiogram was obtained using a Picker 80C ultrasonoscope with a 3·5 MHz transducer (6 mm diameter focused at 7 cm) and a Honeywell fibreoptic strip chart recorder. The examination was performed in the supine position by the method described by Feigenbaum.[4] Each echocardiogram was taken within 12 to 24 hours after blood sampling for renin. The echocardiographic indices obtained were left ventricular end-systolic and end-diastolic dimensions (Fig. 1), mean velocity of circumferential fibre shortening (mean Vcf), per cent shortening of the internal dimension (% SID), and ejection fraction (EF), as previously described.[5–7] Left ventricular systolic time interval (LVSTI), that is left ventricular pre-ejection period (LVPEP), and ejection time (LVET) were measured on the aortic root echo after determination of the aortic cusp opening and closure[8 9] (Fig. 2). The ratio of LVPEP/LVET was calculated and used as an index of left ventricular performance.[9]

Table *Clinical data of patients*

Case no.	*Age (y)*	*Sex*	*Diagnosis*	*Operation*
1	3 1/12	M	TOF+ASD	Total correction
2	1 5/12	M	TOF+ASD	Total correction
3	6 11/12	M	TOF	Total correction
4	6 7/12	M	TOF	Total correction
5	9/12	M	TOF	Total correction
6	1 1/12	M	TOF+ASD	Total correction
7	3 8/12	M	TOF+right aortic arch	Total correction
8	6 2/12	F	TOF+ASD	Total correction
9	2 2/12	M	TOF	Total correction
10	5 8/12	M	PS+bicuspid aortic valve	Pulmonary commissurotomy
11	2 4/12	M	PS+VSD	Pulmonary infundibulotomy patch on VSD
12	2 10/12	M	PS+ASD	Pulmonary commissurotomy
13	7 0/12	F	PS+ASD+ hypoplastic RV	Pulmonary infundibulotomy + patch
14	2 8/12	M	VSD+AR	Closure of VSD
15	3 8/12	F	VSD	Patch on VSD
16	9 9/12	F	ASD (L to R shunt)	Closure of ASD
19	12 2/12	M	MR+MS	Mitral Starr valve
20	15 0/12	F	MR	Mitral Carpentier ring
21	12 11/12	F	MR+MS	Mitral Starr valve
22	6 1/12	M	AR+AS	Aortic Bjork valve

AR, aortic regurgitation; AS, aortic stenosis; ASD, atrial septal defect; MR, mitral regurgitation; MS, mitral stenosis; PS, pulmonary stenosis; RV, right ventricle; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

For the statistical analyses, Student's t tests for paired and unpaired observations and linear regression with correlation were used.

The study procedure was accepted by the Ethical Committee of the Department of Pediatrics.

Results

Systemic arterial blood pressures did not change significantly before and after operation. None of these patients had perturbations of serum electrolyte levels or of the acid-base balance.

PLASMA RENIN ACTIVITY (PRA)

Mean plasma renin activity values for all patients are shown in Fig. 3. We arbitrarily separated patients with tetralogy of Fallot and pulmonary stenosis (group 1) from those with left-to-right shunts and rheumatic valvular heart disease (group 2). Though both groups showed significant differences in age, their preoperative plasma renin activity values did not differ significantly. The mean value in group 1 was 588 fkat per litre, with a range of 42 to 2100 (mean 2·8 ng/ml per hour; range 0·2 to 10), while the mean value in group 2 was 1029 fkat per litre, with a range of 378 to 2226 (mean 4·9 ng/ml per hour; range 1·8 to 10·6).

The preoperative values were within normal limits in all patients.[10 11] On the second postoperative day there was a sharp rise in plasma renin activities in all patients, with a progressive fall towards the 12th day and two months postoperatively, respectively. Compared with the preoperative values, the plasma renin activity was significantly higher on the second (PRA II) ($p<0\cdot01$), on the fifth (PRA III) ($p<0\cdot02$), and on the 12th (PRA IV) ($p<0\cdot05$) postoperative day. There was no correlation between the plasma renin activity and the age of the patients (as previously shown), the change in arterial oxygen saturation, or the change in haematocrit. The patients with high plasma renin activity values had no systemic arterial hypertension, or hypokalaemia. In patients with tetralogy of Fallot and pulmonary stenosis, the mean postoperative values were, however, higher than for the others without

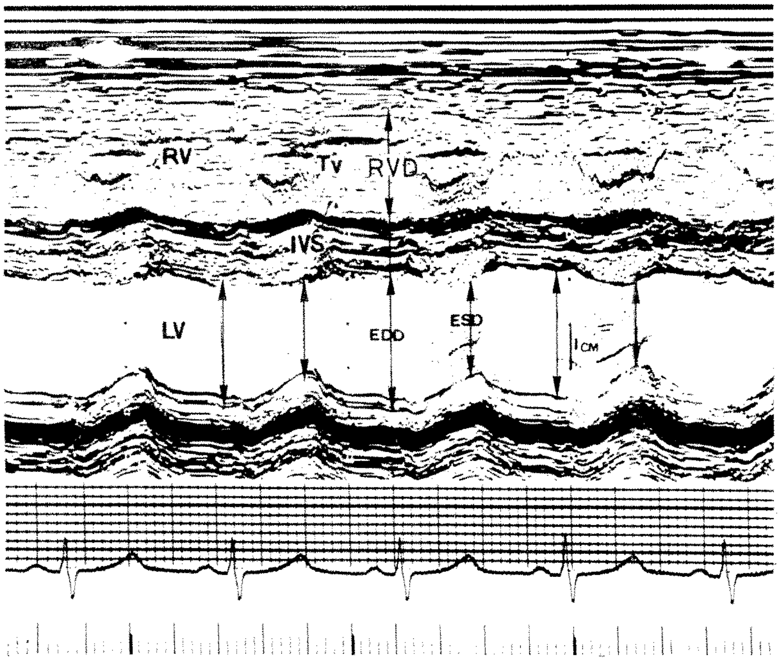

Fig. 1 *Echocardiogram of the right and left ventricle in a patient with tetralogy of Fallot two days after surgical correction. RV, right ventricle; TV, tricuspid valve; LV, left ventricle; IVS, interventricular septum; EDD, end-diastolic dimension; ESD, end-systolic dimension; RVD, right ventricular dimension.*

tetralogy of Fallot, but this difference was significant only on the second postoperative day because of the wide dispersion of individual values.

ECHOCARDIOGRAM

In patients with rheumatic valvular heart disease and those with significant left-to-right shunts, the left atrium was very dilated before operation. This dilatation decreased after surgical correction and the left atrium approached normal size soon after the intervention. The left atrial diameter was smaller than normal in patients suffering from tetralogy of Fallot, pulmonary stenosis, or atrial septal defect before operation. After the operation,

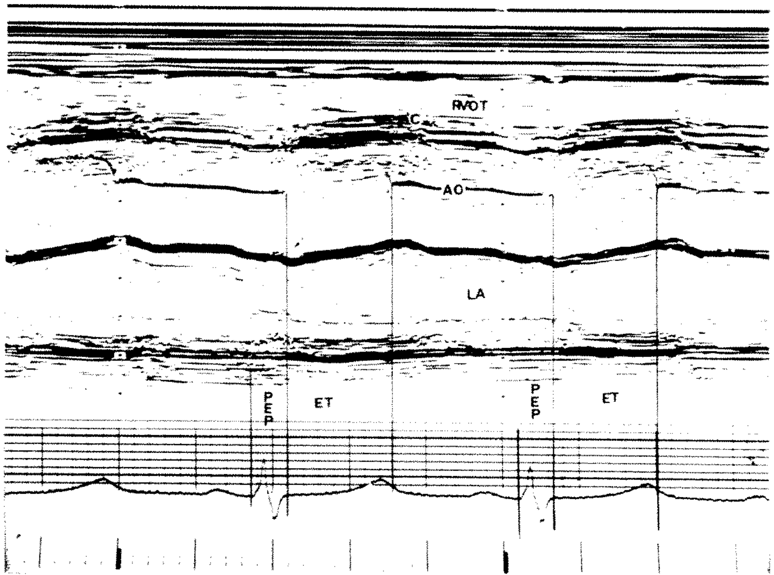

Fig. 2 *Aortic valve echocardiogram of a patient with tetralogy of Fallot two days after operation. C, catheter in the right ventricle; RVOT, right ventricular outflow tract; Ao, aorta; LA, left atrium; PEP, left ventricular pre-ejection period; ET, left ventricular ejection time.*

there was a pronounced and rapid increase of left atrial dimension.

The same group of patients also had smaller left ventricular diameters before operation than normal. After corrective surgery these dimensions increased progressively, and finally reached normal diameters two months after operation (Fig. 4). The changes were highly significant as we had shown previously.[7] Those patients who suffered from rheumatic valvular disease or from other congenital malformations with dilated left ventricles before operation, showed a decrease in left ventricular diameters after operation (Fig. 4).

Indices of left ventricular function were calculated from left ventricular dimensions and LVSTI; the results are shown in Fig. 5a, b, c. The percentage SID of the left ventricle showed only insignificant changes throughout the postoperative period in patients with tetralogy of Fallot and pulmonary stenosis, whereas the other patients had significantly diminished values on the second postoperative day with a subsequent progressive return to normal values. The mean Vcf and the ejection fraction showed a similar pattern of changes.

Patients with tetralogy of Fallot and pulmonary stenosis maintained normal values of LVPEP/LVET ratios, postoperatively, whereas in the other patients an increase of LVSTI ratio and abnormally high values on the second and fifth postoperative days were seen. This increase was probably a result of poor left ventricular contractility. With increasing time after surgery they returned towards normal values (two months after the intervention).

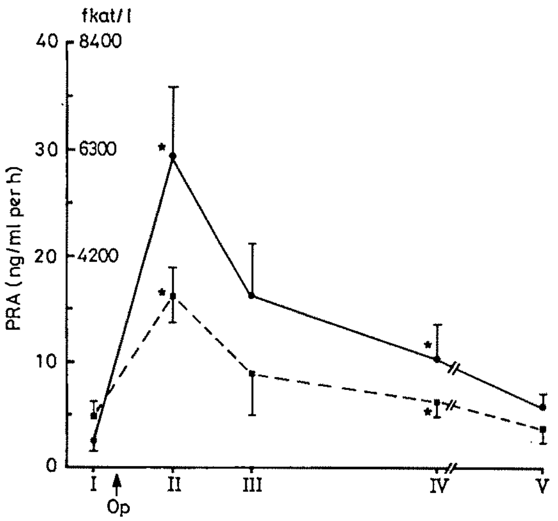

Fig. 3 *Sequential plasma renin values (mean ±SEM):* (●) *in patients with tetralogy of Fallot and pulmonary stenosis;* (■) *in patients with rheumatic heart disease and left-to-right shunts; I, preoperative values; II, III, IV, values on the second, fifth, and 12th postoperative days; V, six to eight weeks after operation; Op, operation; *, significant.*

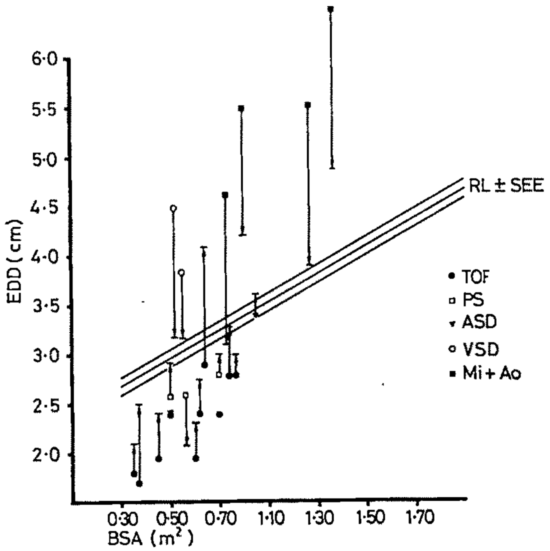

Fig. 4 *Nomogram of the end-diastolic diameter (EDD) of the left ventricle according to Epstein* et al. *in* Circulation *1975;* **51:** *1124–9.*
(RL, regression line + SEE). The preoperative diameters of the left ventricle (LVEDD) in each patient is shown: TOF, tetralogy of Fallot; PS, pulmonary stenosis; ASD, atrial septal defect; VSD, ventricular septal defect; Mi, Ao, mitral and aortic valve disease (rheumatic heart disease). The tip of the arrow indicates the measurement on the fifth postoperative day in each patient. Tetralogy of Fallot and pulmonary stenosis show an increase in LVEDD while VSD, Mi, and Ao show a decrease in LVEDD.

RENIN VALUES VS ECHOCARDIOGRAPHIC DATA

The relation between plasma renin activity values and echocardiographic indices was analysed by plotting the plasma renin activity of a given patient on a given day against his echocardiographic dimensions and function indices obtained on the same day. No correlation was found between plasma renin activity values and per cent shortening of the internal dimension values, mean Vcf, or LVPEP/ET ratio, and changes in left atrial dimensions. For each patient, the differences between the preoperative end-diastolic dimension and the end-diastolic dimension on the second, fifth, and 12th postoperative days were calculated, that is the postoperative increase or decrease in dimension. This difference was expressed as a percentage of the preoperative end-diastolic dimension value (% change EDD) and was compared with the corresponding postoperative renin value. On the second postoperative day, all patients were in cardiac failure with distinctly raised plasma renin activity values and inconsistent changes in left ventricular dimensions. Therefore no correlations between plasma renin activity values and echocardiographic indices were calculated on that day. There was a significant linear correlation from the fifth postoperative day between the logarithm of the plasma renin activity values and the percentage change in end-diastolic dimension. The patients with a small ventricle that dilates postoperatively tended to have higher plasma renin activity values than the patients with a larger ventricle which decreased in size after surgery. The correlation is shown for the fifth and the 12th postoperative day in Fig. 6a and b.

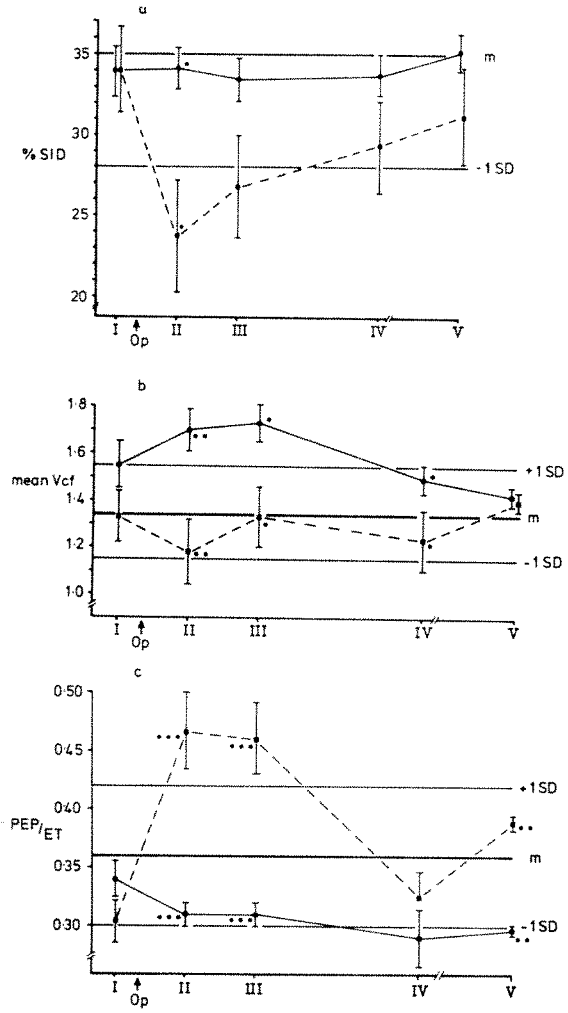

Fig. 5 *Left ventricular function indices in patients with tetralogy of Fallot and pulmonary stenosis (●), and in patients with rheumatic heart disease and left-to-right shunts (■). I, preoperative values; II, III, IV, values on the second, fifth, and 12th postoperative day; V, six to eight weeks postoperatively;* (a) *per cent shortening of the internal dimension (% SID, mean ±SD);* (b) *mean velocity of circumferential fibre shortening (mean Vcf, mean ±SD);* (c) *PEP/ET = left ventricular systolic time-interval ratio. The horizontal lines indicate the normal values ±1SD. Patients with tetralogy of Fallot and pulmonary stenosis show only slightly impaired function indices; patients with rheumatic heart disease and left-to-right shunt lesions show significant changes in cardiac function.*

Discussion

An increase in the activity of the renin-angiotensin system was previously reported to follow open heart surgery with cardiopulmonary bypass in adults.[12] In studies with measurement of plasma renin activity, the wide dispersion of individual values is to be taken into consideration. These variations, which are important in normal children,[13] are even more obvious in patients who receive cardiotonic and/or diuretic treatment for cardiac failure.[14] This explains the relatively great scatter of plasma renin activity values during the postoperative period.

In the present study we observed a distinct increase in plasma renin activity on the second postoperative day in all patients. This increase could be a result of cardiopulmonary bypass,[12] aortic clamping, as well as fluid restriction,[15] diuretics,[14 16] and cardiotonics.[17–19] Plasma renin activity values, however, remained high on the fifth and 12th postoperative day in all patients and were significantly higher in patients operated on for tetralogy of Fallot and pulmonary stenosis. The difference between the two groups cannot be explained by the type of surgery and the time on cardiopulmonary bypass. Changes in renal function (renal plasma flow and glomerular filtration rate) were not observed after cardiac surgery,[1] and, therefore, could not account for the changes in plasma renin activity. The persistence of high values on the fifth and 12th postoperative day, as well as the differences between various cardiac lesions have, to our knowledge, not yet been reported.

Postoperative haemodynamic changes observed by serial echocardiograms might help to explain the prolonged increase of renin-angiotensin activity in tetralogy of Fallot and pulmonary stenosis. Corrective surgery in these patients is followed by an increased pulmonary blood flow but also by altered geometric relation of the ventricles (the left ventricle being pushed backwards by the dilated right ventricle.)[20, 21] While the left atrium dilates rapidly, the left ventricle dilates only slowly over days and weeks.[7] The most important increase in left ventricular size is, however, observed during the first three weeks after operation.

The difference in plasma renin activity between the two groups with the particularly high value of plasma renin activity in tetralogy of Fallot and pulmonary stenosis could be explained by the following hypothesis. Patients with tetralogy of Fallot and pulmonary stenosis are in acute left and right heart failure because of a non-compliant left ventricle and a malfunctioning dilated right ventricle. Acute cardiac failure is known to be accompanied by enhanced sympathetic tone, by increased activity of the adrenergic nervous system, with norepinephrine accumulations in the arterial blood,[22] and by increased activity of the renin-angiotensin system.[18, 19] Patients with rheumatic cardiopathies and shunt lesions are in chronic cardiac failure before operation and are treated with digitalis, diuretics, and a low salt diet, preoperatively. This treatment is continued after corrective surgery. Chronic heart failure is usually not accompanied by increased activity of the renin-angiotensin II system. Therefore, the renin-angiotensin system in patients with rheumatic cardiopathies is more stable. In addition, the left atrial and left ventricular, but also the right ventricular size of these patients diminishes after operation as seen in Fig. 4.

Left ventricular function tests obtained by echocardiography were normal or only slightly impaired in patients with tetralogy of Fallot and pulmonary stenosis while they were more disturbed in the other patients. There was, however, no correlation between the function test and the plasma renin activity, as previously shown by Turini *et al.*[23]

The mechanism controlling the renin release in congestive heart failure has not yet been well defined.[19] Numerous studies suggest that—besides adrenergic system regulating mechanisms—pressure receptors in the heart and great arteries may modify the release of renin. Cardiopulmonary mechanoreceptors might play the most important role.[24–26] The role of these receptors, however, remains questionable, and the published reports are contradictory.[24, 25, 27–32]

Plasma renin activity values decrease when the left ventricle dilates and approaches its normal size in patients with tetralogy of Fallot and pulmonary stenosis (Fig. 6a, b). Increased plasma renin activity values persist, however, certainly until the 12th postoperative day, but are less pronounced at that time since the left ventricle has returned to normal size. In patients with a preoperatively dilated left atrium and dilated left ventricle, plasma renin activity decreases when left atrial and left ventricular size diminishes. These changes in size occur more rapidly and more significantly in the first postoperative days. In both groups of patients the interaction between changes in ventricular size and venous return seems to modulate the renin secretion via different cardiopulmonary receptors.

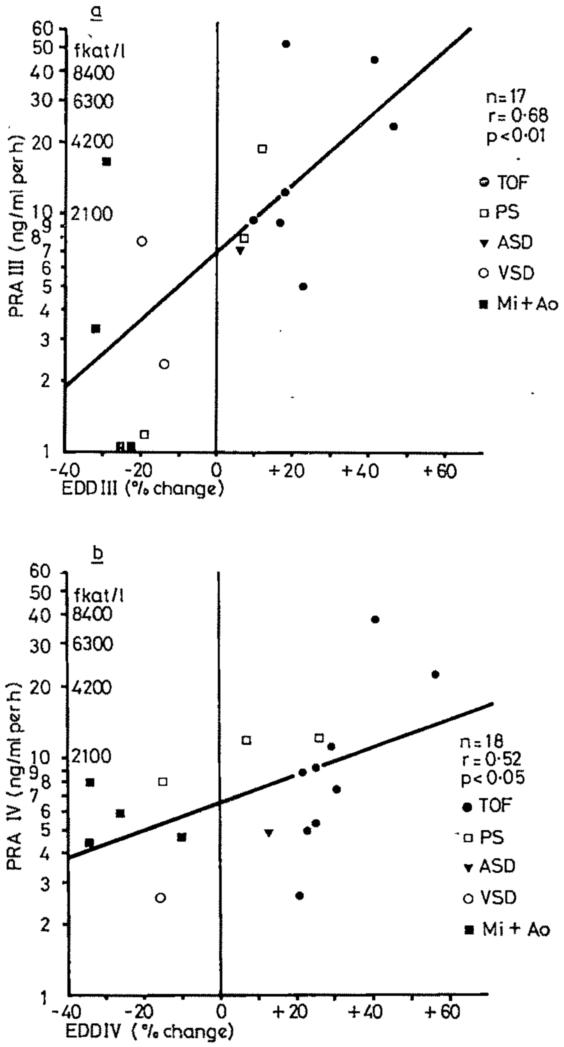

Fig. 6 *Graphic representation of the correlation between plasma renin activity (PRA) and the percentage change between pre- and postoperative LVEDD (% change EDD). Regression lines are indicated.* (a) *On the fifth postoperative day (III)*; (b) *on the 12th postoperative day (IV).*

References

1 Bourgeois BFD, Donath A, Paunier L, Rouge JC. Effects of cardiac surgery on renal function in children. *J Thorac Cardiovasc Surg* 1979; **77:** 283–6.

2 Vallotton MB. Parallel radioimmunoassays of angiotensin I and of angiotensin II for measurement of renin activity and of circulating active hormone in human plasma (abstract). *Horm Metab Res* 1970; Suppl 3: 94.

3 Poulsen K. Simplified method for radioimmunoassay of enzyme system: application on the human renin-angiotensin system. *J Lab Clin Med* 1971; **78:** 309–15.

4 Feigenbaum HL. *Echocardiography*. Philadelphia: Lea & Febiger, 1976.

5 Cooper RH, O'Rourke RA, Karliner JS, Peterson KL, Leopold GR. Comparison of ultrasound and cineangiographic measurements of mean rate of circumferential fiber shortening in man. *Circulation* 1972; **46:** 914–23.

6 Meyer RA, Stockert J, Kaplan S. Echographic determination of left ventricular volumes in pediatric patients. *Circulation* 1975; **51:** 297–303.

7 Oberhänsli I, Friedli B. Echocardiographic study of left and right ventricular dimension and left ventricular function in patients with tetralogy of Fallot, before and after surgery. *Br Heart J* 1979; **41:** 40–53.

8 Hirschfeld ST, Meyer RA, Schwartz DC, Korfhagen J, Kaplan S. Measurement of right and left ventricular systolic time intervals by echocardiography. *Circulation* 1975; **51:** 304–9.

9 Weissler AM, Lewis RP, Leighton RF. The systolic time interval as a measure of left ventricular performance in man. In: Yu PN, Goodwin JF, eds. *Progress in cardiology*. Vol. 1. Philadelphia: Lea & Febiger, 1972: 155–83.

10 Hiner LB, Gruskin AB, Baluarte HJ, Cote ML. Plasma renin activity in normal children. *J Pediatr* 1976; **89:** 258–61.

11 Stalker HP, Holland NH, Kotchen JM, Kotchen TA. Plasma renin activity in healthy children. *J Pediatr* 1976; **89:** 256–8.

12 Taylor KM, Morton IJ, Brown JJ, Bain WM, Caves PK. Hypertension and the renin-angiotensin system following open heart surgery. *J Thorac Cardiovasc Surg* 1977; **74:** 840–5.

13 Dillon MJ, Ryness JM. Plasma renin activity and aldosterone concentration in children. *Br Med J* 1975; **iv:** 316–9.

14 Kaplan NM, Kem DC, Holland OB, Kramer NJ, Higgins J, Gomez-Sanchez C. The intravenous furosemide test: a simple way to evaluate renin responsiveness. *Ann Intern Med* 1976; **84:** 639–45.

15 Kimura, T, Minai, K, Matsui K, *et al.* Effect of various states of hydration on plasma ADH and renin in man. *J Clin Endocrinol Metab* 1976; **42:** 79–87.

16 Zanchetti AS. Neural regulation of renin release. Experimental evidence and clinical implications in arterial hypertension. *Circulation* 1977; **56:** 691–8.

17 Antonello A, Carguielli G, Ferrari M, Melacini P, Montanaro D. Effect of digoxin on plasma-renin activity in man (letter) *Lancet* 1976; **ii:** 850.

18 Franciosa JA, Cohn JN. Hemodynamic responsiveness to short and long term vasodilatators in left ventricular failure. *Am J Med* 1978; **65:** 126–33.

19 Watkins L, Burton JA, Haber E, Cant JR, Smith FW, Barger C. The renin-angiotensin aldosterone system in congestive failure in conscious dogs. *J Clin Invest* 1976; **57:** 1606–17.

20 Laver MB. Right ventricular function: a limiting factor. In: *Zentraleuropäischer Anesthesie-Kongress 1977. Médecine et Hygiène, Genève.* 1979: 263–7.

21 Pontoppidan H, Wilson RS, Rie MA, Schneider RC. Respiratory intensive care. I. Evolution of respiratory care. *Anesthesiology* 1977; **47:** 96–116.

22 Braunwald E. Alterations in the function of the adrenergic nervous system in heart failure. *Bull Eur Physiopathol Respir* 1979; **15:** 881–96.

23 Turini GA, Brunner HR, Ferguson RK, Rivier JL, Gavras H. Congestive heart failure in normotensive man. Haemodynamics, renin and angiotensine II blockade. *Br Heart J* 1978; **40:** 1134–42.

24 Brennan LA Jr, Malvin RL, Jochim KE, Roberts DE. Influence of left and right atrial receptors on plasma concentrations of ADH and renin. *Am J Physiol* 1971; **221:** 273–8.

25 Mancia G, Romero JC, Shepherd JT. Continuous inhibition of renin release in dogs by vagally innervated receptors in the cardiopulmonary region. *Circ Res* 1975; **36:** 529–35.

26 Kiowski W, Julius S. Renin response to stimulation of cardiopulmonary mechanoreceptors in man. *J Clin Invest* 1978; **62:** 656–63.

27 Johnson JA, Davis JO, Gotschall RW, *et al.* Evidence for an intravenal beta receptor in control of renin release. *Am J Physiol* 1976; **230:** 410–8.

28 Thames MD. Reflex suppression of renin release by ventricular receptors with vagal afferents. *Am J Physiol* 1977; **233:** H 181–4.

29 Thames MD, Jarechi M, Donald DE. Neural control of renin secretion in anesthetized dogs. Interaction of cardiopulmonary and carotid baroreceptors. *Circ Res* 1978; **42:** 237–45.

30 Thorén PH. Activation of left ventricular receptors with nonmedullated vagal afferent fibers during occlusion of a coronary artery in the cat. *Am J Cardiol* 1976; **37:** 1046–51.

31 Yun JCH, Delea CS, Bartter FC, Kelly G. Increase in renin release after sinoaortic denervation and cervical vagotomy. *Am J Physiol* 1976; **230:** 777–83.

32 Zehr JE, Hasbargen JA, Kurz KD. Reflex suppression of renin secretion during distention of cardiopulmonary receptors in dogs. *Circ Res* 1976; **38:** 232–9.

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Results of 24 hour ambulatory monitoring of electrocardiogram in 131 healthy boys aged 10 to 13 years*

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SUMMARY Ambulatory monitoring of the electrocardiogram was performed in 131 healthy boys aged between 10 and 13 years for two consecutive periods of 24 hours. When awake the maximal heart rates ranged from 100 to 200 and the minimal from 45 to 80 beats per minute. During sleep maximal rates were 60 to 110 beats and minimal rates 30 to 70 beats per minute. Sinus arrhythmia was seen in every boy and in 36 (27·5%) no other changes were found. Sinuatrial block, Mobitz type I, was not seen. Sinuatrial block, Mobitz type II, occurred twice only. Complete sinuatrial block occurred in 8·4 per cent, never lasted more than one cycle, and was always followed by a junctional beat.

First degree atrioventricular block occurred in 8·4 per cent and Mobitz type I atrioventricular block in 10·7 per cent. Premature beats were always single, atrial in 13 per cent, ventricular in 26 per cent, and except in two boys were never more than four in 24 hours. There were no episodes of ventricular or supraventricular tachycardia.

Changes in P wave morphology were common and slow junctional rhythm occurred in 13 per cent during sleep.

In the past, diagnoses of arrhythmias in childhood were made from the resting surface electrocardiogram taken for short periods, and often depended on chance recordings. Since 24 hour ambulatory monitoring on magnetic tapes became available, the tendency has been to interpret them in the same way as resting electrocardiograms despite the fact that they are recorded with the patient awake or asleep, during exercise or rest, and with the patient in the erect, prone, or supine positions. The findings on 24 hour ambulatory electrocardiographic tape recordings in normal healthy adults have been published.[1-3] So far there are no reports of the findings in normal healthy children. This study was undertaken to define the characteristics of the electrocardiogram over 24 hour periods in normal healthy boys.

Methods

Recordings were made for two consecutive periods of 24 hours in 131 healthy boys whose ages ranged from 10 to 13 years. The boys had no symptoms and were questioned particularly about fainting attacks or loss of consciousness. A full clinical examination was carried out by one of us (O S) and no cardiac abnormality was detected in any of the subjects.

One chest electrode was placed on the upper part of the sternum and the other in the position of chest lead V4. They were firmly fixed to the skin without any air trap, taped down, and connected to a battery-operated Oxford Instruments miniature analogue tape recorder. The cassette was housed in a leather bag worn round the waist. Diaries were kept by the boys who noted their activities at particular times and the time of going to bed so that these could be correlated with findings on the tapes. They led normal lives and continued all usual sports except swimming. Analysis was carried out using the Oxford Medical Systems Analyser which automatically detects changes in heart rate or rhythm from preset RR intervals. The equipment incorporated a "synclock" mechanism to avoid variations in tape speed which would produce artefactual rhythm or rate patterns. Printouts were made of any abnormalities and at

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four hourly intervals throughout the trace for 10 second periods even when no abnormality was found.

The heart rate was recorded from the tapes at 30 minute intervals. The rate varied at each recording. It is important to state that none of the lowest or highest rates ever lasted more than half an hour.

In 17 of the 131 boys (13%) the initial recordings were unsatisfactory. In four the electrodes were displaced, in eight the leads were broken; five of the tapes had been unwound by the boys and damaged. All were repeated and satisfactory tracings obtained; our observations are reported as mean ranges over 24 hours.

The following observations were made from the analysis of each tape:

(1) The highest and lowest heart rates, awake and asleep.

(2) Sinus arrhythmia (a gradual increase and decrease in PP intervals).

(3) Abnormal P waves during the day and night, their duration, and the heart rates associated with abnormal P waves. When abnormal P waves occurred over three or more successive beats, this was defined as junctional rhythm.

(4) *Sinuatrial block*. This was classified using conventional criteria.[4–6] In *Type I* PP intervals are equal but occasional beats are dropped; the interval between the P waves surrounding the dropped beat is less than that of two cycles (Mobitz type I sinuatrial block). In *Type II* the interval between the P waves surrounding a dropped beat is equal to twice the PP interval between normal beats (Mobitz type II sinuatrial block).

Complete sinuatrial block in which there is failure of impulse formation in the sinuatrial node, or if the impulse is formed it is not conducted into the atrium.

(5) *First degree heart block* (a PR interval of 0·20 s or more).

(6) *Second degree heart block*. This was subdivided into two groups.

(a) Type I (Wenckebach phenomenon) (Mobitz type I). A dropped beat occurring after progressive increase in the PR interval.

(b) Type II (Mobitz type II) in which a dropped beat occurred without any changes in the PR interval.

(7) The presence of premature beats, ventricular or atrial.

Results (Table 1)

Of the 131 boys, 36 showed no abnormalities and remained in sinus rhythm throughout the recording.

(1) HEART RATES

The lowest and highest heart rates are shown in Fig. 1a during sleep and Fig. 1b when awake. The maximal heart rates ranged from 100 to 200 beats per minute when awake. The high rate of 200 occurred in only one patient and was a sinus tachycardia. The minimal rates were from 45 to 80. During sleep maximal rates ranged from 60 to 110 and the minimal rates from 30 to 70 beats per minute.

(2) SINUS ARRHYTHMIA

This was present in every tracing and sinus pauses as long as 1·6 s occurred in six subjects at night when the heart rates were slow. The presence of sinus arrhythmia caused some difficulty when interpreting abnormalities such as second degree block type I (Wenckebach) and finding varying PP intervals in addition (Fig. 2).

(3) ABNORMAL P WAVES

Changes in the form of P waves occurred in 44 boys (33·6%), during sleep only in 20 (15·2%), when awake only in seven (5·3%); in three the P wave changed during exercise. In 17 boys (13%) the P waves altered during the day and night, usually becoming inverted or flat. In 17 (13%) the abnormal P waves were associated with junctional rhythm (Fig. 3), varying from three successive beats to periods of 25 minutes. During sleep the junctional rhythm was associated with slow heart rates.

(4) SINUATRIAL BLOCK

Mobitz type I sinuatrial block was not seen. Mobitz type II sinuatrial block was seen twice only and occurred only twice in each boy during sleep (Fig. 4). Complete sinuatrial block was seen in 11 boys (8·4%). The block lasted for one cycle only, was always followed by junctional beats, and in

Table 1 *Summary of findings on 24 hour electrocardiograms in 131 healthy boys aged 10 to 13 years*

Rhythm at lowest heart rates	Sinus	114
	Junctional	17
Sinuatrial block with junctional escape		11
First degree atrioventricular block		11
Second degree atrioventricular block		
Mobitz type I		14
Mobitz type I (2:1 block)		1
Premature beats	Atrial	10
	Ventricular	34

two was followed by slow junctional rhythm (Fig. 3). It never occurred more than three times over a 24 hour period, and in two subjects it occurred once only. In three patients the block occurred during the day, in six at night, and in two both day and night.

(5) FIRST DEGREE HEART BLOCK

This occurred in 11 (8·4%) of the 131 boys, in seven (5·3%) during sleep only. In four of these, Mobitz type I atrioventricular block developed during sleep, with heart rates between 40 and 55 per minute (Table 2).

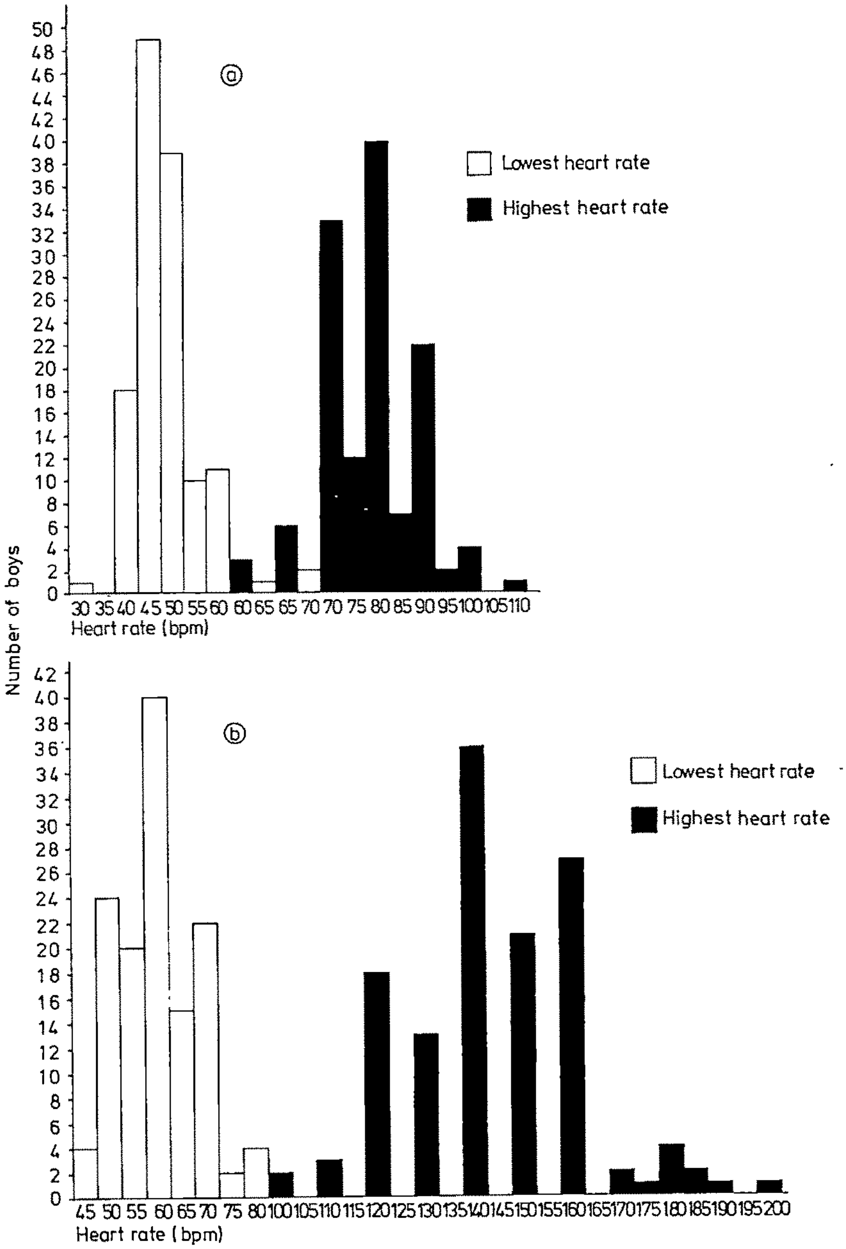

Fig. 1 *Lowest and highest heart rates* (a) *during sleep,* (b) *while awake.*

(6) SECOND DEGREE ATRIOVENTRICULAR BLOCK

Type I (Wenckebach) occurred in 14 boys (10·7%) (Fig. 2), 12 at night, and two during the day. Four of these also had first degree heart block while asleep. The heart rates during the periods of block varied from 40 to 60 per minute. The frequency of occurrence of the block varied from two to four times in 24 hours except in one boy in whom it occurred 54 times over 24 hours; 2:1 block was seen in one boy during sleep and occurred only once (Fig. 5). Type II (Mobitz II) was not seen.

(7) PREMATURE BEATS

Single premature ventricular beats occurred in 34 boys (26%), in 20 while awake only, in six of these during exercise. In seven boys they were evident during sleep only and in seven during sleep and when awake. The number of premature beats in 24 hours was between one and four except in two boys, one of whom had 35 premature beats in 24 hours including a period of coupling lasting for nine seconds. The other had 27 premature beats over 24 hours. In one boy the premature beats were unifocal but in the others where more than one occurred, they were multifocal. Atrial premature beats occurred in 10 boys (13%). They were always single, in four during sleep, in six when awake. There were never more than two in 24 hours except in one boy who had two half-hour periods of coupling during sleep.

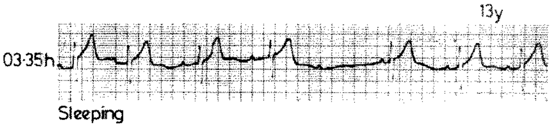

Fig. 2 *Sinus bradycardia with sinus arrhythmia (cycle length 96 to 124) and type I second degree block (Wenckebach).*

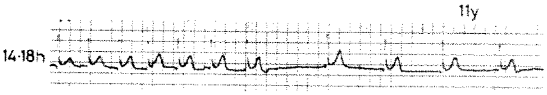

Fig. 3 *Complete sinuatrial block, sinus rhythm, then pause greater than preceding cycle lengths. Subsequent P waves poorly defined—slow junctional rhythm.*

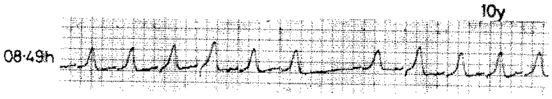

Fig. 4 *Mobitz type II sinuatrial block. Shortening of PR interval after the pause is probably related to length of time allowed for recovery of atrioventricular conduction—it gradually lengthens again.*

Table 2 *First degree heart block*

PR interval (s)		*Lowest heart rate during sleep*	*Frequency of Mobitz type I second degree block*
Awake	*Asleep*		
0·12	0·3	40	One episode during sleep
0·18	0·24	48	One episode during sleep
0·21	0·22	44	Twice during sleep
0·22	0·30	40	54 times during sleep
0·14	0·24	40	
0·10	0·21	40	
0·18	0·22	44	
0·14	0·21	54	
0·12	0·24	45	
0·14	0·21	45	
0·12	0·21	55	

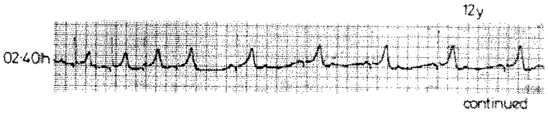

Fig. 5 *Second degree (2:1) atrioventricular block.*

Discussion

It is essential that the normal 24 hour electrocardiogram in healthy children is defined before we try to make definitive diagnoses from it in symptomatic children. Such data have not previously been reported in children. Data from adults cannot be applied to children.

The slow rates which occur in healthy boys are of importance. Our values of minimal heart rates when awake are similar to those in male medical students[1] but the range is greater than found in studies in adults aged 16 to 65 years.[2 3] Presumably the slow rates during sleep are the result of increased vagal tone and sympathetic withdrawal. Such episodes of bradycardia during a 24 hour period should not be regarded as indicating sinus node disease.

Complete sinuatrial block never lasted more than one cycle so the occurrence of longer periods of sinus arrest is likely to be significant, particularly if associated with the classical history of syncope on extreme exertion suggestive of sinus node disease in the young. Our tracings were measured carefully for evidence of Mobitz type I sinuatrial block but it was not seen.

First degree atrioventricular block was always associated with bradycardia, especially during sleep. Second degree atrioventricular block Mobitz type I was a surprising finding and was commoner in our series (10·7%) than in the series of 50 medical students (6%)[1] and than in older age groups (2·3%)[2]. In another series of adults it was not seen.[3] It was always associated with bradycardia and occurred at night in 12 of 14 boys. Again increased vagal tone causing depression of the atrioventricular nodal conduction was probably responsible. This Wenckebach atrioventricular block has also been reported in Olympic athletes[7]; 2:1 block occurred once (Fig. 5). Mobitz type II atrioventricular block was not seen.

The occurrence of premature beats and their incidence over 24 hours was much less frequent in boys of 11 to 13 years than in adults. The R-on-T phenomenon was never seen nor were episodes of ventricular or supraventricular tachycardia both of which have been observed in healthy adults (16 to 65 years).[2 3]

Alteration in form and direction of P waves in the standard resting electrocardiogram is uncommon. Our impression when we first used 24 hour ambulatory recordings that such changes in P wave morphology were common has been confirmed. It is important not to overinterpret the significance of these changes when the recording is from a single lead and the patient's position is changing.

From the clinical point of view the results of this study are helpful. It seems that runs of premature beats are likely to be of pathological significance in this age group, as are episodes of ventricular or supraventricular tachycardia. Complete sinus arrest lasting more than one cycle is likely to be abnormal. Second degree atrioventricular block Mobitz I (Wenckebach phenomenon) cannot be regarded as evidence of disease; its association with bradycardia suggests that it is probably a manifestation of increased vagal tone. Sinus bradycardia and changes in P wave morphology on 24 hour recordings cannot be regarded as evidence of sinus node dysfunction. These findings on the standard electrocardiogram recorded at rest have been listed as suggestive evidence of sinus node dysfunction[8] but the dynamic single lead 24 hour recordings cannot be interpreted in the same way. Further studies are required in other age groups and are at present in progress in boys aged between 14 and 16 years.

References

1 Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. *Am J Cardiol* 1977; **39:** 390–5.

2 Clarke JM, Hamer J, Shelton JR, Taylor S, Venning GR. The rhythm of the normal human heart. *Lancet* 1976; **ii:** 508–12.

3 Kostis JB, Moreyra AE, Natarajan N, *et al.* Ambulatory electrocardiography: what is normal? (abstract). *Am J Cardiol* 1979; **43:** 420.

4 Krikler DM, Curry PVL. Electrocardiographic features of cardiac arrhythmias. In: Hamer J, ed. *Recent advances in cardiology.* London, Edinburgh, New York: Churchill Livingstone, 1977: 81–101.

5 WHO/ISC Task Force. Definition of terms related to cardiac rhythm. *Am Heart J* 1978; **95:** 796–806.

6 Zipes DP. Second degree atrioventricular block. *Circulation* 1979; **60:** 465–72.

7 Meytes I, Kaplinsky E, Yahini J, Hanne-Paparo N, Neufeld HN. Wenckebach A-V block: a frequent feature following heavy physical training. *Am Heart J* 1975; **90:** 426–30.

8 Scott O, Macartney FJ, Deverall PB. Sick sinus syndrome in children. *Arch Dis Child* 1976; **51:** 100–5.

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Br Heart J 1980; **44:** 309–16

Left ventricular function in Friedreich's ataxia*

An echocardiographic study

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SUMMARY Left ventricular function was assessed in seven patients with Friedreich's ataxia using computer-assisted analysis of the left ventricular echocardiograms and compared with those of 45 normal children matched for age and sex. The left ventricle in Friedreich's ataxia was symmetrically hypertrophied, cavity dimension was normal or small, and septal motion and peak velocity of circumferential shortening were normal in all patients. In diastole the duration of rapid filling was normal, peak rate of increase in left ventricular dimension was reduced in two patients, mitral valve opening was delayed with respect to minimum cavity dimension in seven, and there were significantly greater than normal increases in left ventricular dimension during the isovolumic period to mitral valve opening in seven, indicating abnormal and incoordinate relaxation. Peak rates of posterior wall systolic thickening and diastolic thinning were reduced in four and six patients, respectively, whereas peak rates of septal systolic thickening and diastolic thinning were reduced in one and four, respectively, suggesting a disproportionately greater impairment of the posterior wall than of septal function.

The absence of asymmetric septal hypertrophy and mid-systolic closure of the aortic valve, the presence of normal septal motion, and the greater reduction in posterior wall than in septal dynamics are inconsistent with previous ideas that the heart disease of Friedreich's ataxia is identical to hypertrophic cardiomyopathy.

Computer-assisted analysis of echocardiograms permits recognition of heart disease in Friedreich's ataxia before the onset of cardiac symptoms or development of clinical signs of heart disease.

Friedreich's ataxia is a rare spinocerebellar neuromyelopathy, usually transmitted as an autosomal recessive.[1] It is characterised by the early onset of progressive ataxia, dysarthria, posterior column signs in the lower limbs, and muscle weakness.[2 3] Though myocardial involvement in Friedreich's ataxia is well documented and many patients die from heart failure,[4 5] cardiovascular symptoms and signs usually develop late in the course of the disease.[6] Clinical examination is complicated because (1) auscultatory abnormalities occur only in a minority[6–8]; (2) radiographic evidence of cardiomegaly is uncommon[8] and may be difficult to assess in the presence of coexistent scoliosis[2]; and (3) a wide range of non-specific electrocardiographic abnormalities occurs.[9]

Previous echocardiographic studies have shown no constant abnormality. Thus left ventricular dimension can be normal or small, left ventricular hypertrophy concentric or asymmetric, and systolic anterior movement of the mitral valve may or may not be present. Haemodynamic and angiographic studies have shown similar variability in left ventricular function with and without left ventricular outflow tract obstruction.[10–13] Since there appear to be no specific diagnostic features by which cardiac involvement in Friedreich's ataxia may be recognised, we used computer-assisted analysis of left ventricular echocardiograms in an attempt to determine whether any abnormalities of regional

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or cavity function were consistently present, which might enable earlier recognition of cardiac disease, and possibly prove useful in the reassessment of patients at periodic follow-up.

Subjects

NORMALS

Left ventricular echocardiograms were recorded in 45 clinically normal schoolchildren (24 girls and 21 boys) aged from 9 to 15 years (mean age 12 years) in order to obtain normal values for septal, posterior wall, and left ventricular internal dimensions in subjects of this age. Fifteen of these echocardiograms (eight female and seven male) were digitised to provide normal data for septal, posterior wall, and left ventricular cavity dynamics which were used as a basis for comparison with that recorded from the children with Friedreich's ataxia.

PATIENTS WITH FRIEDREICH'S ATAXIA

Left ventricular echocardiograms were recorded from seven children (three girls and four boys) aged from 9 to 15 years (mean age 12 years) (Fig. 1). The diagnosis of Friedreich's ataxia was established clinically and supported by electromyography in all seven patients who were referred for cardiac assessment by the division of neurology at the Mayo Clinic where they all attended for regular follow-up. Two of the patients were sibs and one other patient had a sib with Friedreich's ataxia, but the latter was not available for echocardiographic examination. All patients were in sinus rhythm at the time of examination, and none was taking any drugs known to affect myocardial performance.

Methods

ECHOCARDIOGRAPHIC RECORDINGS

Echocardiograms were obtained with an Ekoline 20 Ultrasonoscope using a 2·25 MHz transducer with a repetition frequency of 1000 cycles/s. Recordings were made on a Cambridge Scientific Instruments multichannel strip-chart recorder at paper speeds of 50 to 100 mm/s, with simultaneous electrocardiograms. Echoes of the right and left sides of the septum and the endocardium and epicardium of the posterior left ventricular wall were obtained at the level of the mitral valve. Echocardiograms were only accepted for analysis when these echoes were clear and continuous throughout the cardiac cycle. Echocardiograms were digitised[14] using a Science Accessories Corporation Graf pen and processed by a Control Data 3500 computing system. Data points were generated for both right and left sides of the septum, and the endocardial and epicardial surfaces of the posterior left ventricular wall, so that strings of XY co-ordinates were obtained for the four surface boundaries. The echoes were calibrated with points defining a time interval of 2000 ms, a depth of 4 cm, and two

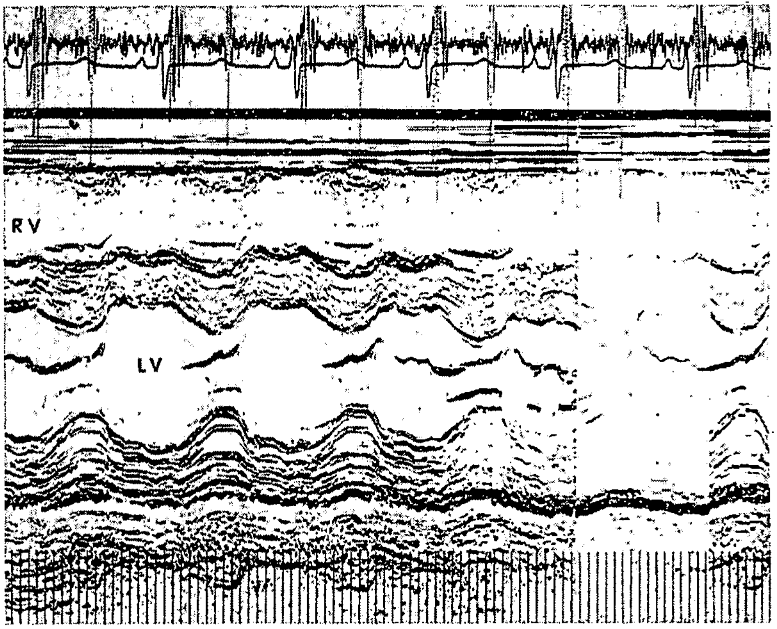

Fig. 1 *Echocardiogram of patient with Friedreich's ataxia showing right ventricle, interventricular septum, left ventricular cavity, and posterior wall, with electrocardiogram and phonocardiogram at top.*

successive Q waves on the electrocardiogram enclosing the cardiac cycle to be analysed. Plots were made of continuous left ventricular cavity, septal, and posterior wall dimensions, and their rates of change expressed either in cm/s, or normalised to refer to unit cavity dimension, or septal and posterior wall thickness. From these plots (Fig. 2 and 3) the following measurements were made.

(1) *Dimensions*

(a) Maximum and minimum left ventricular cavity dimensions.
(b) Percentage left ventricular cavity shortening.
(c) Maximum and minimum posterior wall thicknesses.
(d) Maximum and minimum septal thicknesses.
(e) Ratio of minimum septal to minimum posterior wall thicknesses.

(2) *Systolic left ventricular function*
Normalised velocities:
(a) Normalised peak rates of left ventricular cavity dimension change.
(b) Normalised peak rates of posterior wall thickening.
(c) Normalised peak rates of septal thickening.

(3) *Diastolic left ventricular function*
Time intervals:
(a) Time from minimum left ventricular cavity dimension (when the first derivative of cavity dimension changed from negative to positive) to the onset of mitral valve opening, defined as the initial separation of the mitral valve cusps.
(b) Time from mitral valve opening to the discontinuity on the plot of continuous left ventricular cavity dimension (taken as the point in time at which the left ventricular rate of

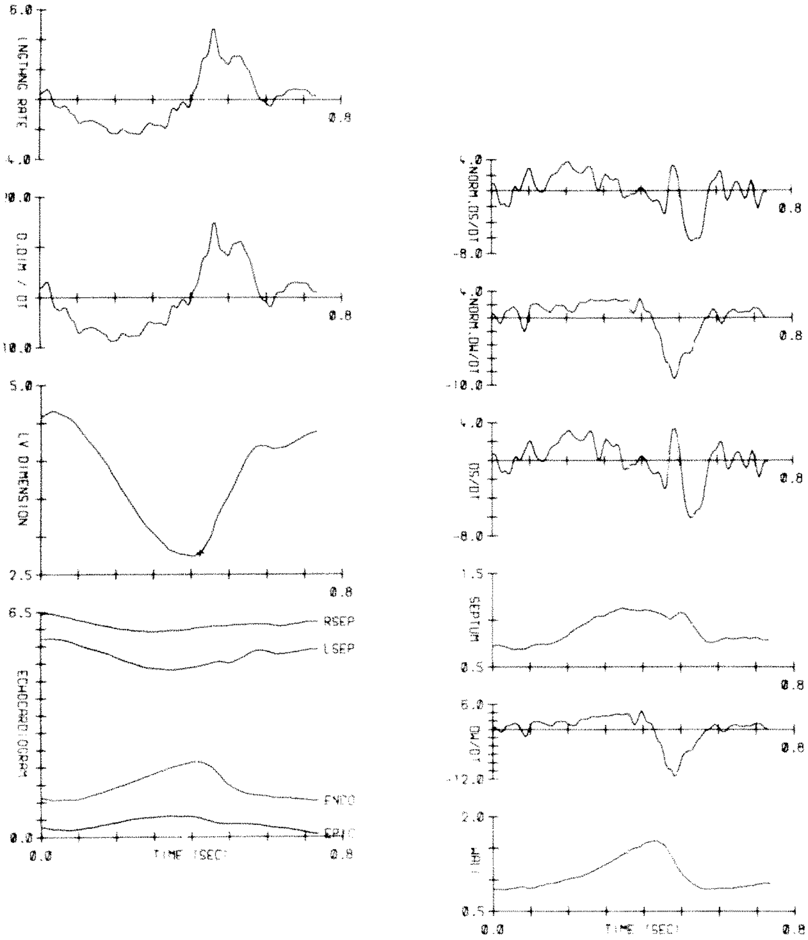

Fig. 2 *Normal child. Set of computer plots from the digitised echocardiogram reproduced in lowest panel on left. Above it are plots of continuous left ventricular dimension, its rate of change and its normalised rate of change, respectively. On the right panel—continuous posterior left ventricular wall dimension at bottom, above its rate of change, continuous septal dimension, and its rate of change, normalised rate of change of wall thickness, and at top normalised rate of change of septal thickness. (X denotes timing of mitral valve opening.)*

increase in dimension dropped abruptly to 20 per cent of its peak value) which represents the true rapid filling period.

Change in left ventricular dimension during the following time interval:

Change in left ventricular cavity dimension during the time interval between minimum left ventricular dimension and mitral valve opening expressed as a percentage of the total change in left ventricular dimension occurring from end-systole to end-diastole.

Velocities of dimension change:

(a) Peak rate of increase in left ventricular dimension.
(b) Normalised peak rates of posterior wall thinning.
(c) Normalised peak rates of septal thinning.

Results

DIMENSIONS

The 95 per cent confidence limits for maximum and minimum left ventricular internal dimensions percentage shortening, maximum and minimum septal and posterior wall thicknesses, and the ratio of minimum septal to minimum posterior wall thicknesses are shown for the normal children in Table 1, and represent the mean values plus and minus 2 standard deviations from the mean.

Maximum and minimum internal left ventricular dimensions in the patients with Friedreich's ataxia were significantly reduced in five of seven (<95% confidence limits) and normal in two of seven. However, percentage left ventricular cavity shortening and septal motion were normal in all patients. The septum and posterior wall in all patients with Friedreich's ataxia were hypertrophic in so far as their minimum thicknesses were either at or in excess of the 95 per cent confidence limits for normal children of the same age and sex (Table 1, Fig. 1 and 2). Maximum septal and posterior wall thicknesses were normal in all except two children in whom both were increased, and the ratio of minimum septal to minimum posterior wall thick-

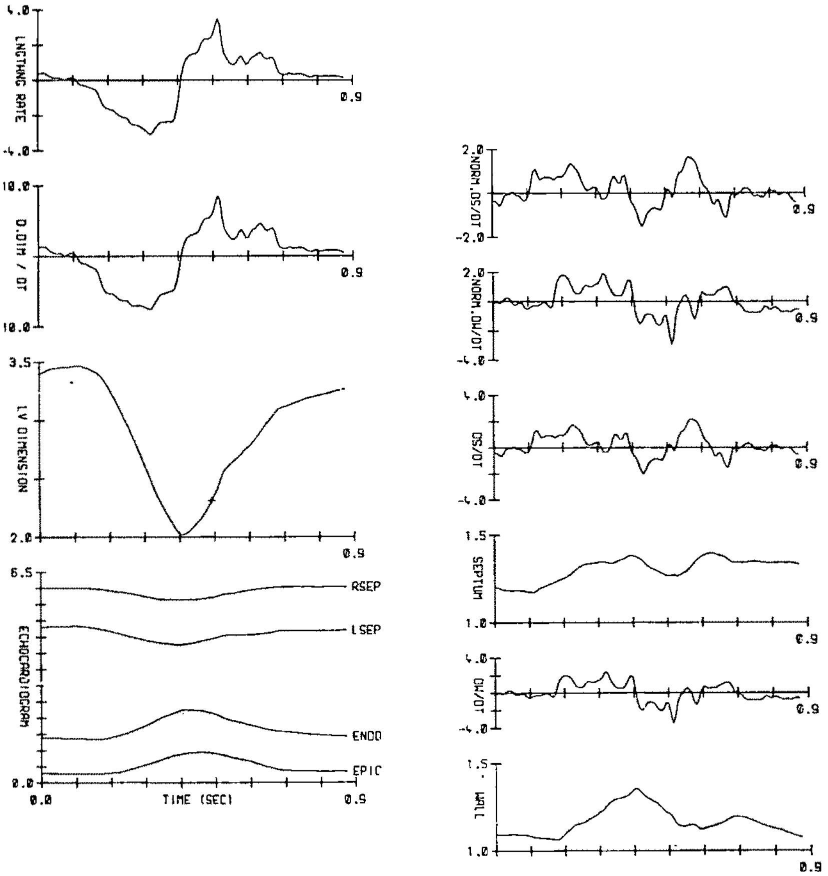

Fig. 3 *Friedreich's ataxia. Set of plots laid out as in Fig. 2. Note reduction in peak rate of increase in left ventricular dimension during diastole, delay in mitral valve opening (X), with respect to minimum dimension and in addition reduced normalised peak rates of septal and posterior wall thickening and thinning.*

Table 1 *Echocardiographic measurements of left ventricular dimensions*

Case no.	*LV cavity dimensions (cm)*		*Per cent cavity shortening*	*Septal dimensions (cm)*		*Posterior LV wall dimension (in.)*		*Ratio of minimum septal to minimum PW thickness*
	Max	*Min*		*Max*	*Min*	*Max*	*Min*	
1	3·7	1·8	51	1·4	1·[illegible]	1·9	0·9	1·2
2	3·3	1·6	52	1·4	1·[illegible]	1·7	1·1	1·0
3	3·2	1·1	65	1·5	1·2	1·9	1·1	1·1
4	3·2	1·6	50	1·3	0·9	1·5	0·9	1·0
5	2·8	1·6	43	1·2	1·0	1·4	1·0	1·0
6	4·0	2·6	35	1·4	1·[illegible]	1·5	1·1	1·0
7	3·5	2·0	43	1·5	1·3	1·4	1·1	1·2
Mean	3·4	1·8	47	1·4	1·[illegible]	1·6	1·0	1·1
Normals (n = 45)	4·5 ±0·5	2·8 ±0·3	39 ±5	1·1 ±0·2	0·7 ±0·1	1·2 ±0·2	0·7 ±0·1	1·0 ±0·1
Normal range mean ±28·0	3·7 to 5·3	2·3 to 3·4	29 to 49	0·7 to 1·5	0·5 to 0·9	0·8 to 1·6	0·5 to 0·9	0·8 to 1·2

nesses was 1·1 indicating that the left ventricular hypertrophy was concentric (Table 1).

SYSTOLIC LEFT VENTRICULAR FUNCTION

Normalised peak rates of increase in left ventricular cavity dimension or peak V_{CF} were normal in all patients with Friedreich's ataxia (Table 2, Fig. 3). Normalised peak rates of septal thickening were within normal limits in all except one patient in whom it was reduced, while peak rates of systolic thickening of the posterior wall were significantly reduced in four of seven patients (Table 2), indicating a greater impairment of systolic function of the posterior wall than of the septum.

DIASTOLIC LEFT VENTRICULAR FUNCTION

Time intervals

The time interval from minimum left ventricular cavity dimension to mitral valve opening was significantly prolonged in all patients—the delay varying from 63 to 90 ms longer than in the normal children (Table 2).

The duration of true rapid filling represented by the time from mitral valve opening to the discontinuity on the left ventricular dimension plot, when the rate of change of dimension had fallen to 20 per cent of its peak value, was normal in all patients (Table 2).

Changes in left ventricular dimension before mitral valve opening

Changes in left ventricular cavity dimension during the short time interval between minimum left ventricular dimension and mitral valve opening in the normal children (0 to 15 ms), before the phase of rapid filling, were very small and amounted to no more than 7 per cent of the total increase occurring from end-systole to end-diastole (Table 2, Fig. 2). By contrast in the patients with Friedreich's ataxia, not only was this time interval prolonged,

Table 2 *Echocardiographic assessment of left ventricular function*

Case no.	*Peak V_{CF} 5 to 1*	*MVO (ms)*	*Peak dD/dt (diastolic) (cm/s)*	*Rapid diastolic filling period (ms)*	*Per cent increase in LV dimension from minimum down to MVO*	*Normalised peak rate of systolic thickening of septum and posterior wall*		*Normalised peak rate of diastolic thinning of septum and posterior wall*	
1	3·8	63	11·0	163	17	2·1	3·9	1·9	6·2
2	4·1	81	10·0	127	13	2·7	4·1	1·8	3·4
3	4·3	90	12·0	112	22	2·2	2·1	3·0	4·0
4	3·7	61	9·0	167	16	3·1	4·0	2·8	3·7
5	3·4	73	7·8	215	17	2·2	2·3	2·0	3·9
6	2·4	80	8·2	192	2[illegible]	2·2	2·0	3·1	2·7
7	2·3	87	6·8	227	14	1·5	2·3	1·2	1·8
Mean	3·4	76	9·3	172	17	2·2	2·9	2·3	3·6
Normals (n = 15)	3·1 ±0·5	11 ±6	13·5 ±2·4	176 ±34	0 to 7	3·1 ±0·6	3·8 ±0·7	3·6 ±0·7	6·8 ±1·3
Normal range mean ±28·0	2·1 to 4·1	0 to 23	8·3 to 18·3	112 to 224	0 to 7	1·9 to 4·3	2·4 to 5·2	2·2 to 5·0	4·2 to 9·4

but there were significantly greater increases in left ventricular dimension of up to 22 per cent (Table 2, Fig. 3).

Velocities of dimension change

Peak rates of increase in left ventricular dimension during diastole were significantly reduced in two patients, at the lower limits of normal in two further children with Friedreich's ataxia, but in the middle of the normal range in three.

Normalised peak rates of septal thinning were significantly reduced in four patients and normal in three, while the peak rates of posterior wall thinning were below the 95 per cent confidence limits in six of seven patients (Table 2). These results indicate that not only is the septal function impaired in fewer patients than the posterior wall, but also that diastolic thinning of the septum and posterior wall is more frequently reduced than their respective peak rates of systolic thickening.

CLINICAL FINDINGS

Six of the seven patients had no symptoms referable to the cardiovascular system, and one had chest pain suggesting angina. On physical examination five patients had grade 2/4 ejection systolic murmurs at the left sternal border, and these were the only abnormal clinical cardiac signs. Three patients had moderate kyphoscoliosis (Table 3).

Chest *x*-ray film showed a normal heart size (cardiothoracic ratio <0·5) and normal pulmonary vasculature in all patients. Electrocardiograms showed sinus rhythm in all cases, and the only abnormal findings were non-specific T wave changes in three patients, which were present in the inferior or anterolateral leads. There were no abnormalities of intraventricular conduction and no evidence of left ventricular hypertrophy (Table 3).

The one patient with angina had systolic anterior motion of the mitral valve echocardiographically. At cardiac catheterisation there was no left ventricular outflow tract gradient at rest, but a gradient of 20 to 30 mmHg with isoprenaline.

There was no apparent relation between left ventricular cavity, septal, or posterior wall dynamics, and clinical or electrocardiographic signs; and none of these measurements was of any value in identifying the patient with angina or systolic anterior motion of the mitral valve.

Discussion

The incidence of clinical heart disease in Friedreich's ataxia is well documented, and has been reported to vary from 50 to 90 per cent,[7–9] though abnormal myocardial fibre morphology and extensive interstitial fibrosis were present in 100 per cent of the hearts examined at necropsy.[4 15] Though most patients with Friedreich's ataxia die from heart failure or cardiac arrhythmia rather than from neurological causes,[5] the nature and aetiology of the left ventricular disease remains unresolved. It was initially suggested that the underlying myocardial lesion was hypertrophic cardiomyopathy,[6 16] because asymmetric septal hypertrophy[16] and systolic anterior motion of the mitral valve[5] were described echocardiographically, and because in a few patients left ventricular outflow tract obstruction was documented haemodynamically.[10 12 13 17] Few attempts, however, have been made to assess left ventricular function in Friedreich's ataxia or indeed to identify abnormalities which might enable early recognition of cardiac involvement in this disease, which is somewhat surprising since heart failure accounts for more than 50 per cent of the deaths. Echocardiographic studies are limited in number and have been confined to enumerating qualitatively abnormal features such as asymmetric septal hypertrophy and systolic anterior motion of the mitral valve in spite of the fact that this technique lends itself especially well to repeated left ventricular function studies in children and young adults in whom this disease predominates.[3] Cardiac catheter studies have shown that myocardial dysfunction is

Table 3 *Clinical findings*

Case no.	*Signs*	*Cardiac symptoms*	*Electrocardiogram*	*Chest radiograph*	
				Heart size	*Kyphoscoliosis*
1	Ejection systolic murmur 2/4	None	Inverted T waves II, III, aVF	N	+
2	Ejection systolic murmur 2/4	None	N	N	N
3	Ejection systolic murmur 2/4	Chest pain ? angina	Inverted T waves V4–6	N	N
4	Ejection systolic murmur 2/4	None	N	N	N
5	None	None	N	N	N
6	Ejection systolic murmur 2/4	None	Inverted T waves II, III, aVF	N	+
7	None	None	N	N	+

almost invariable, as indicated by the raised left ventricular end-diastolic pressure and reduced contractility angiographically,[10 12 13 17] and that left ventricular outflow tract obstruction is rare.[10 17]

The present study showed that left ventricular internal dimensions in Friedreich's ataxia are either reduced or normal, and that normal percentage shortening is preserved because of the universal presence of normal septal motion. The reduction in left ventricular cavity size is accounted for by the increased septal and posterior wall thicknesses compared with age- and sex-matched normal subjects, and, in contrast to previous reports,[6 16] the left ventricular hypertrophy was concentric and not asymmetric as shown by the ratio of minimum septal to posterior wall thicknesses, which was close to unity.

Systolic rates of inward wall movement assessed in terms of peak velocity of circumferential fibre shortening, peak V_{CF}, were normal in all patients with Friedreich's ataxia. In spite of this, however, abnormalities of systolic function were detectable in that the peak rates of systolic thickening of the posterior wall were significantly reduced compared with normal in more than half the patients, while septal thickening was only abnormal in one patient. These results suggest that in this disease there is a disproportionately greater impairment of systolic function of the posterior wall than of the septum.

An independent manifestation of left ventricular disease which has been little recognised until recently is diastolic dysfunction, which may even develop before systolic abnormalities occur.[18 19] Diastolic abnormalities, however, other than static pressure-volume characteristics, are less accessible to measurement than systolic or pump function, but are made readily available with computer-assisted analysis of echocardiograms. Using this technique, we found diastolic abnormalities of left ventricular function in all patients with Friedreich's ataxia, and a constant feature was the significant delay in mitral valve opening with respect to minimum left ventricular dimension, events which were synchronous in normal children. The duration of the true rapid diastolic filling period was normal in all patients, though the peak rate of increase in left ventricular dimension during diastole was significantly reduced in two patients to a degree observed in left ventricular inflow tract obstruction caused by moderate mitral stenosis.[14] However, this disturbance of left ventricular filling was not a result of obstruction at mitral valve level since mitral valve echoes were entirely normal and must therefore reflect reduced rates of outward wall movement caused by abnormal left ventricular relaxation. Further evidence of abnormal diastolic function was provided by the significantly greater than normal increases in left ventricular dimension during the isovolumic period between minimum left ventricular dimension and mitral valve opening, which must represent abnormal cavity shape changes resulting from incoordinate relaxation. That myocardial diastolic function in Friedreich's ataxia is abnormal is also corroborated by previous reports of increased left ventricular end-diastolic pressure with normal cavity volume,[10 11 17] indicating increased stiffness and reduced distensibility. In addition, peak rates of septal and posterior wall thinning were significantly reduced in the majority of patients though this reduction occurred more commonly in the posterior wall than in the septum, and these changes were detectable even when the peak rate and duration of cavity filling were normal. These more frequent diastolic abnormalities of cavity, septal, and posterior wall function suggest that relaxation more readily loses its high degree of organisation than does contraction, becoming not only slow but incoordinate, while systolic function may remain normal, or only become abnormal later. This late development of contraction abnormalities may in part explain the delay in appearance of cardiac signs and symptoms in this disease, which moreover vary independently of the severity and rate of progression of the neurological disorder.

The aetiology of the left ventricular dysfunction in Freidreich's ataxia remains unresolved. However, in contrast to previous reports,[6 16] the left ventricle is unlike that in hypertrophic cardiomyopathy in so far as the septum was not hypokinetic, septal motion was normal in all patients, left ventricular hypertrophy was concentric and not asymmetric, systolic anterior motion of the mitral valve was uncommon and mid-systolic aortic valve closure was absent. In addition, reduction in peak rates of systolic thickening and diastolic thinning were both more pronounced in the posterior wall than in the septum which is the reverse of that occurring in hypertrophic cardiomyopathy. Furthermore, histological examination of the hearts in Friedreich's ataxia showed severe interstitial fibrosis which is no more frequent in hypertrophic cardiomyopathy than in normal hearts[20 21] and fibre disarray, which may be regarded as the hallmark of hypertrophic cardiomyopathy[22] was absent.[15]

Left ventricular function in Friedreich's ataxia also differed conspicuously from that in dystrophia myotonica, another neurocardiac disorder, in which there was early and important impairment of systolic function demonstrable as reduced peak V_{CF} and ejection fraction.[23] It also was different from that in Duchenne's muscular dystrophy in which myocardial function is well preserved.[24]

This preponderance of diastolic abnormalities, with maintenance of relatively normal systolic function, also occurs in association with left ventricular hypertrophy secondary to systemic hypertension and aortic stenosis[25] and, therefore, they could theoretically be a manifestation of left ventricular hypertrophy in Friedreich's ataxia. However, it seems more likely that, with the inexorable and rapid deterioration of left ventricular function in Friedreich's ataxia, resulting in death in the second and third decades, it relates more to the replacement of myocardial fibres with non-contractile fibrous tissue—a florid and invariable histological finding—than simply to left ventricular hypertrophy which in any case was not extremely severe.

Patients such as these are not only of theoretical interest because of the appearance of diastolic rather than systolic abnormalities, but they are also of practical diagnostic value in that (1) myocardial involvement in Friedreich's ataxia may be recognised earlier and reassessed at follow-up, and (2) such abnormalities provide early evidence of the clinical syndrome described as heart failure.

References

1 Andermann E, Remillard GM, Goyer C, *et al.* Genetic and family studies in Friedreich's ataxia. *Can J Neurol Sci* 1976; **3:** 287–301.
2 Geoffroy G, Barbeau A, Breton G, *et al.* Clinical description and roentgenologic evaluation of patients with Friedreich's ataxia. *Can J Neurol Sci* 1976; **3:** 279–86.
3 Walton JN. *Brain's diseases of the nervous system.* 7th ed. London: Oxford University Press, 1969: 589.
4 Hewer RL. Study of fatal cases of Friedreich's ataxia. *Br Med J* 1968; **iii:** 649–52.
5 Van der Hauwaert LG, Dunmoulin M. Hypertrophic cardiomyopathy in Friedreich's ataxia. *Br Heart J* 1976; **38:** 1291–8.
6 Smith ER, Sangalang VE, Heffernan LP, Welsh JP, Flemington CS. Hypertrophic cardiomyopathy: the heart disease of Friedreich's ataxia. *Am Heart J* 1977; **94:** 428–34.
7 Cote M, Davignon A, Pecko-Drouin K, *et al.* Cardiological signs and symptoms in Friedreich's ataxia. *Can J Neurol Sci* 1976; **3:** 319–21.
8 Boyer SH IV, Chisholm AW, McKusick VA. Cardiac aspects of Friedreich's ataxia. *Circulation* 1962; **25:** 493–505.
9 Thorén C. Cardiomyopathy in Friedreich's ataxia: with studies of cardiovascular and respiratory function. *Acta Paediatr (Stockholm)* [Suppl] 1964; **153:** 1–136.
10 Cote M, Davignon A, Elias G, *et al.* Hemodynamic findings in Friedreich's ataxia. *Can J Neurol Sci* 1976; **3:** 333–6.
11 Ruschhaupt DG, Thilenius OG, Cassels DE. Friedreich's ataxia associated with idiopathic hypertrophic subaortic stenosis. *Am Heart J* 1972; **84:** 95–102.
12 Gach JV, Andriange M, Franck G. Hypertrophic obstructive cardiomyopathy and Friedreich's ataxia: report of a case and review of literature. *Am J Cardiol* 1971; **27:** 436–41.
13 Soulié P, Vernant P, Gaudeau S, *et al.* Le coeur dans la maladie de Friedreich: étude hemodynamique droite et gauche. *Mal Cardiov* 1966; **7:** 369–86.
14 Gibson DG, Brown D. Measurement of instantaneous left ventricular dimension and filling rate in man, using echocardiography. *Br Heart J* 1973; **35:** 1141–9.
15 Hewer RL. The heart in Friedreich's ataxia. *Br Heart J* 1969; **31:** 5–14.
16 Smith ER, Flemington CS, Heffernan LP, *et al.* Asymmetric septal hypertrophy: the cardiomyopathy of Friedreich's ataxia (abstract). *Clin Res* 1975; **23:** 805.
17 Guerin R, Elias G, Davignon A, *et al.* Cardiac angiographic findings in Friedreich's ataxia. *Can J Neurol Sci* 1976; **3:** 337–42.
18 Upton MT, Gibson DG, Brown DJ. Echocardiographic assessment of abnormal left ventricular relaxation in man. *Br Heart J* 1976; **38:** 1001–9.
19 St John Sutton MG, Tajik AJ, Gibson DG, Brown DG, Seward JB, Givliani AR. Echocardiographic assessment of left ventricular filling and septal and posterior wall dynamics in idiopathic hypertrophic subaortic stenosis. *Circulation* 1978; **57:** 512–20.
20 St John Sutton MG, Anderson KR, Lie JT, Frye RL. Specificity and topography of fiber disarray and fibrosis in hypertrophic obstructive cardiomyopathy (abstract). *Circulation* 1977; **55 & 56,** suppl III: 205.
21 Anderson KR, St John Sutton MG, Lie JT. Histopathological types of cardiac fibrosis in myocardial disease. *J Pathol* 1979; **128:** 79–85.
22 Maron BJ, Ferrans VJ, Henry WL, *et al.* Differences in distribution of myocardial abnormalities in patients with obstructive and non-obstructive asymmetric septal hypertrophy (ASH): light and electron microscopic findings. *Circulation* 1974; **50:** 436–46.
23 Venco A, Saviotti M, Besana D, Finardi G, Lanzi G. Non-invasive assessment of left ventricular function in myotonic muscular dystrophy. *Br Heart J* 1978; **40:** 1262–6.
24 Ahmad M, Sanderson JE, Dubowitz V, Hallidie-Smith KA. Echocardiographic assessment of left ventricular function in Duchenne's muscular dystrophy. *Br Heart J* 1978; **40:** 734–40.
25 Gibson DG, Traill TA, Hall RJC, Brown DJ. Echocardiographic features of secondary left ventricular hypertrophy. *Br Heart J* 1979; **41:** 54–9.

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Non-invasive diagnosis in clinically suspected atrial septal defect of secundum or sinus venosus type

Value of combining chest x-ray, phonocardiography, and M-mode echocardiography

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SUMMARY Twenty-three consecutive patients with clinical (auscultatory and electrocardiographic) signs of uncomplicated atrial septal defect of secundum or sinus venosus type were examined by chest *x*-ray, phonocardiography, and echocardiography, before right heart catheterisation. Seventeen (74%) had atrial septal defect, two patients (9%) had insignificant pulmonary stenosis, and four subjects (17%) were normal. No false positive diagnosis of atrial septal defect was made by chest *x*-ray examination, whereas increased vascular markings were incorrectly interpreted as pulmonary congestion in one case. Four patients had *x*-ray films showing questionable signs of left-to-right shunt. Six of 15 patients with a large left-to-right shunt were correctly selected for surgery based on radiological findings. One false negative but no false positive diagnosis of atrial septal defect was made by phonocardiography. Four cases with and four cases without atrial septal defect were classified as having questionable phonocardiographic signs of atrial septal defect. Echocardiographic distinction between those with atrial septal defect and those without atrial septal defect was correct in all cases; quantitative measurement of left-to-right shunt, however, was unsatisfactory. Combined normal findings by *x*-ray film and echocardiography appeared adequate in all cases for the exclusion of atrial septal defect (six patients). When the six patients who were correctly identified for surgery from the radiological findings are included, there was a total of 12 patients out of 23 (52%: 95% confidence limits 31 to 73%) who were evaluated definitively by the non-invasive tests.

The patient with fixed splitting of the second heart sound on auscultation, incomplete right bundle-branch block, and a normal electrocardiographic QRS axis frequently presents a diagnostic problem. Though suspicion of an atrial septal defect of the secundum or sinus venosus type in such patients will often prove justified, heart catheterisation in others will disclose no signs of atrial septal defect or any other structural abnormality.[1] New techniques such as two-dimensional contrast echocardiography,[2 3] ultrasonic Doppler examination,[4] and radionuclide methods[5] may become future routine examinations in suspected atrial septal defect. At present, however, chest *x*-ray examination, phonocardiography, and M-mode echocardiography are well established non-invasive techniques readily available in most cardiac centres.[6–8] The purpose of the present study was to investigate the reliability of these techniques in the setting of clinically suspected uncomplicated atrial septal defect.

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Patients and methods

During a one year period 23 consecutive patients with a clinical suspicion of atrial septal defect were referred for heart catheterisation. There were 14 male and nine female patients, range 5 to 48 years, mean 15 years. The patients were defined by a fixed splitting of the second heart sound on auscultation accompanied by a grade 1–2/6 systolic ejection murmur in the pulmonary area and incomplete or complete (case 17, Table) right bundle-branch block with a normal QRS axis. Patients suspected of pulmonary hypertension or structural abnormalities other than atrial septal defect were excluded from the study, based on physical examination and electrocardiogram. The day before heart catheterisation non-invasive examinations including chest *x*-ray, phonocardiography, and M-mode echocardiography were carried out and evaluated separately by three different observers. Each examiner was unaware of the results of the two other tests.

Chest x-*ray* examination was performed in the erect position in the posteroanterior and lateral projections. Signs of increased pulmonary blood flow in patients with fixed splitting of the second heart sound and incomplete right bundle-branch block were considered diagnostic of atrial septal defect. Thus, patients with intrapulmonary vessels in the upper lung zones of increased calibre and readily visible to the peripheral edge of the lungs were classified as having atrial septal defect.[6] Atrial septal defect requiring operation (see below) was diagnosed in those cases with intrapulmonary vessels of increased calibre in all lung zones.[6] Equivocal findings were denoted as questionable atrial septal defect or questionable atrial septal defect requiring surgery, respectively.

Phonocardiography, with patients in 40° recumbent position, was recorded during normal quiet respiration in the second left intercostal space at a paper speed of 100 mm/s (Siemens-Elema Mingograph 62). A splitting of the second heart sound (A_2P_2 interval) of more than 35 ms during normal expiration in combination with a variation in the splitting (A_2P_2 variation) of less than 15 ms during normal respiration were considered diagnostic of atrial septal defect.[7 8]

Patients with A_2P_2 interval of 30 ± 5 ms or A_2P_2 variation of 20 ± 5 ms, respectively, were classified as questionable atrial septal defect.

Echocardiography was recorded using either Aloka SSD-110 or Mediscan 30 ultrasonic apparatus interfaced to a Cambridge recorder. M-mode scans from apex to base were performed in the supine and left lateral positions with the transducer in the third, fourth, and fifth left intercostal spaces near the sternal border. A paper speed of 25 mm/s was used, whereas interventricular septal motion was studied at the chordal level using 50 or 100 mm/s. Right ventricular end-diastolic dimension was measured in the supine position at the chordal level according to Feigenbaum[8] using the intercostal space with the largest right ventricular end-diastolic dimension (RVD). Measurements were corrected for body surface area (RVD Index = RVD/m^2 body surface). In the clinical context of this series, right ventricular volume overload was regarded as diagnostic of atrial septal defect and defined as the combination of abnormal septal motion[10 11] and right ventricular dilatation (RVD Index of more than 1·4 cm/m^2). A case with an RVD Index more than 1·4 cm/m^2 together with normal septal motion, or abnormal septal motion in a patient with an RVD Index of less than 1·4 cm/m^2 was classified as questionable atrial septal defect. The type of septal motion[10 11] was noted in all scans, but was evaluated definitively from the intercostal space with the largest right ventricular end-diastolic dimension. An M-mode scan from the tricuspid to the mitral valve was performed in each intercostal space in the supine and left lateral positions. The maximum diastolic separation of the tricuspid and of the mitral leaflets was measured in each tracing and their ratio (T/M) calculated according to Chiotellis *et al.*[12] Maximum T/M and maximum RVD Index were correlated to shunt size as determined by catheterisation.

Heart catheterisation was performed percutaneously via the right femoral vein. Pulmonary-to-systemic flow ratio was calculated by the oximetric method.[13] If no left-to-right shunt was demonstrable on oximetry the atrial septum was carefully probed to exclude a communication (two cases) or the hydrogen appearance time was measured.[14]

Patients with a flow ratio equal to or larger than 2·0 or a flow ratio larger than 1·8 in combination with cardiac enlargement were referred for operation.[13]

Results

A left-to-right shunt at atrial level was shown in 17 patients (74%) while six patients (26%) had no detectable atrial septal defect (Table). The left-to-right shunt was small in two patients (flow ratio = 1·3 and 1·5, respectively). The six patients without atrial septal defect included four with normal findings at right heart catheterisation and two patients with negligible valvular pulmonary stenosis (Table).

CHEST *x*-RAY

No false positive diagnosis of left-to-right shunt was made on chest *x*-ray. An increased flow pattern in a 48-year-old man was erroneously interpreted as pulmonary congestion (case 17, Table). Four cases with flow ratios ranging from 1·5 to more than 4 were classified as having questionable signs of left-to-right shunt, whereas a left-to-right shunt was predicted in a patient with a flow ratio of only 1·3. Six patients out of 12 with definite radiological signs of left-to-right shunt were correctly suggested as needing operation according to our present guidelines.[13] The other six patients included three with questionable signs of a large shunt and three patients who were classified as having atrial septal defect not requiring operation, but, of the last-mentioned, two patients had flow ratios of more than 2·0 and were in fact referred for operation (Table).

PHONOCARDIOGRAPHY

Mean A_2P_2 interval ($\pm$SD) in patients with atrial septal defect was $50{\cdot}3 \pm 11{\cdot}3$ ms; this was not significantly different from A_2P_2 interval in patients without atrial septal defect ($40{\cdot}8 \pm 12{\cdot}4$ ms; $p > 0{\cdot}1$; t test). Corresponding values of A_2P_2 variation were $10{\cdot}0 \pm 9{\cdot}2$ ms in patients with atrial septal defect in contrast to patients without atrial septal defect who had A_2P_2 variation $= 25{\cdot}8 \pm 7{\cdot}3$ ms ($p < 0{\cdot}01$; t test). One false negative (flow ratio 1·5) but no false positive diagnosis was made by phonocardiography (Table). Four cases with and four cases without atrial septal defect were classified as questionable.

ECHOCARDIOGRAPHY

Patients with atrial septal defect had RVD Index $= 2{\cdot}8 \pm 0{\cdot}6$ cm/m^2 (mean $\pm$SD), range 2·0 to 4·0 cm/m^2, in contrast to RVD Index $= 1{\cdot}1 \pm 0{\cdot}2$ cm/m^2, range 0·9 to 1·4 cm/m^2, in patients without atrial septal defect ($p < 0{\cdot}001$; t test). The localisation of the largest right ventricular end-diastolic dimension varied; it was obtained in the third intercostal space in six patients, in the fourth intercostal space in nine patients, and in the fifth intercostal space in eight patients. No false negative or false positive diagnosis was made (Table). The maximum ratio

Table *Radiological, phonocardiographic, echocardiographic, and right heart catheterisation findings in 23 patients with clinical suspicion of atrial septal defect of secundum or sinus venosus type (ASD)*

Case no.	*Age (y)*	*Sex*	*X-ray*		*Phono*			*Echo*				*Catheterisation*			
			ASD	*Op*	*A_2P_2 (ms)*	*A_2P_2-var (ms)*	*ASD*	*RVDI (cm/m²)*	*T/M*	*Smot*	*ASD*	*RVP (mmHg)*	*PAP (mmHg)*	*FR*	*Pathology*
1	5	M	+	+	60	0	+	4·0	1·3	B/N	+	30/3	18/8	2·5	Sinus venosus defect, one abn pulm vein
2	8	M	+	?	50	0	+	2·6	1·6	A/B	+	26/4	24/8	1·8	Secundum defect (requiring operation)
3	8	M	+	+	50	10	+	2·7	1·7	A/A	+	34/5	20/8	3·0	Sinus venosus defect
4	8	M	+	—	50	0	+	4·0	1·4	A/N	+	25/6	20/10	3·4	Secundum defect, one abn pulm vein
5	9	F	+	+	60	10	+	2·7	1·6	A/A	+	30/0	20/4	4·0	Secundum defect
6	9	M	+	—	35	20	?	2·9	1·4	B/N	+	52/4	50/8	1·3	Secundum defect, one abn pulm vein, peripheral pulmonary artery stenoses
7	10	F	?		40	0	+	2·6	1·5	B/N	+	30/6	20/8	2·7	Sinus venosus defect, one abn pulm vein
8	11	M	+	?	50	10	+	2·6	1·5	B/N	+	26/6	25/8	2·3	Secundum defect
9	11	F	+	?	50	20	?	2·1	1·5	B/B	+	40/5	27/8	2·3	Secundum defect
10	12	M	?		60	0	+	2·0	1·2	N/B	+	38/6	20/7	2·1	Secundum defect
11	13	M	+	+	50	10	+	2·9	1·5	B/A	+	26/5	20/7	2·2	Sinus venosus defect, one abn pulm vein
12	13	F	?		50	10	+	3·8	2·5	A/A	+	46/4	26/8	> 4·0	Secundum defect
13	17	F	+	—	50	10	+	2·0	1·5	A/A	+	27/4	22/7	2·7	Secundum defect
14	18	F	+	+	25	25	?	2·2	1·4	A/B	+	28/7	27/10	3·0	Sinus venosus defect, two abn pulm veins
15	25	F	+	+	45	15	?	3·0	1·4	A/B	+	28/8	28/10	2·3	Secundum defect
16	33	M	?		50	30	—	2·3	1·3	B/B	+	31/3	24/8	1·5	Secundum defect
17	48	M	—		80	0	+	3·0	1·5	A/B	+	30/9	30/10	3·4	Secundum defect
18	12	F	—		35	25	?	1·0	0·9	N/N	—	32/4	14/8	1	Small PS
19	14	F	—		40	30	—	1·4	1·2	N/B	—	36/5	18/8	1	Small PS
20	15	M	—		40	20	?	1·2	1·0	N/N	—	27/3	24/8	1	Normal
21	15	M	—		50	20	?	0·9	0·9	N/N	—	30/6	26/10	1	Normal
22	17	M	—		60	20	?	0·9	1·1	N/N	—	26/3	22/6	1	Normal
23	20	M	—		20	40	—	1·2	1·2	N/N	—	23/3	23/9	1	Normal

A, A type of abnormal interventricular septum motion; A_2P_2, interval between aortic and pulmonary component of second heart sound measured during normal expiration; A_2P_2-var, variation in splitting of second heart sound during normal respiration; B, B type of abnormal interventricular septum motion; FR, pulmonary-to-systemic flow ratio; N, normal interventricular septum motion; Op, signs of large left-to-right shunt requiring operation; PAP, pulmonary artery pressure; PS, valvular pulmonary stenosis; RVP, right ventricular pressure; RVDI, right ventricular end-diastolic diameter corrected for body surface area; Smot, type of interventricular septum motion; letter to the left of the diagonal stroke signifies septum motion in maximum RVD, whereas letter to the right represents septum motion found in one or more other projections. T/M, maximum ratio between largest opening of the tricuspid and mitral valve; +, present; —, absent.

between tricuspid and mitral leaflet separation (T/M) was 1.5 ± 0.3 (mean $\pm$SD) in patients with atrial septal defect and 1.1 ± 0.1 in patients without ($p < 0.001$; t test). A linear relation could be shown between flow ratio and T/M ($T/M = 0.25 \times FR + 0.85$; $r = 0.80$) and between RVD Index and flow ratio ($\text{RVD Index} = 0.65 \times FR + 0.95$; $r = 0.73$). Patients with small left-to-right shunts (cases 6 and 16, Table) could not be specifically identified; these patients, however, had small T/M values (Table). Septal motion varied within the same individual in most patients with atrial septal defect (Table). Normal motion was observed in either the third or fifth intercostal space in five patients with atrial septal defect.

Discussion

Though right heart catheterisation in older children and adults is a relatively simple procedure carrying only a minimal risk, it would of course be desirable to avoid this examination in healthy subjects with a clinical suspicion of atrial septal defect. Moreover, non-invasive identification of surgical candidates would save time and reduce costs. In our series, chest *x*-ray examination appeared satisfactory in excluding left-to-right shunt. Only one false negative interpretation was made. Increased vascular markings in this case were erroneously regarded as pulmonary congestion (case 17, Table); the patient, however, would of course not have been acquitted of heart disease on the basis of the radiological findings. Furthermore, combination of the radiological findings with phonocardiography and echocardiography would immediately have corrected the radiological diagnosis.

No false positive radiological diagnosis was suggested, but only questionable signs of left-to-right shunt were described in four out of 17 patients with atrial septal defect including three patients with flow ratios of 2·1, 2·7, and more than 4, respectively. Radiological markings suggesting need for operation seemed reliable; however, only six out of 15 such patients were identified. The radiological suggestion of a small atrial septal defect, on the other hand, correlated poorly with catheterisation data; one patient was correctly regarded as having a small shunt, whereas two patients with large shunts were erroneously classified as having small atrial septal defects not requiring operation.

Considering the setting including an auscultatory wide fixed splitting of the second heart sound, the phonocardiographic measurements of A_2P_2 interval and A_2P_2 variation provided relatively poor supplementary information for the exclusion of atrial septal defect in an individual patient as only two out of six patients could be excluded. All patients with A_2P_2 variation below 15 ms had atrial septal defect (12 out of 17 patients with atrial septal defect). These findings are in accordance with previous reports.[7 9] Combining the results of these reports with our data, no better discriminating level of A_2P_2 variation than the value actually selected could be established. It is not surprising that exact measurement of the A_2P_2 interval was of minor value in the differentiation between atrial septal defect and non-atrial septal defect in these patients, who were initially defined by a wide splitting of the second heart sound on auscultation.

Echocardiography distinguished between uncomplicated atrial septal defect and non-atrial septal defect. The RVD Index limit of 1·4 cm/m^2 has been chosen based on published reports[8 10 11 15] and on experiences from our own laboratory. The RVD Index in combination with the pattern of septal motion appeared to be a good discriminator in our series. Other reports have shown the occasional appearance of a patient with atrial septal defect and a normal echocardiogram. These cases were all patients with small left-to-right shunts (flow ratio less than 2·0) or patients with pulmonary hypertension.[11 16 17] One should, however, be aware of a possible false negative echocardiogram. Moreover, echocardiograms indicating right ventricular volume overload in two normal patients have been reported.[1] Thus, the addition of supportive information from phonocardiogram and chest *x*-ray examination is advisable.

Previous reports have shown either no or relatively poor correlation between RVD Index and flow ratio.[10–12] The good correlation in our series may be the result of the consistent use of the largest right ventricular end-diastolic dimension. We have very limited data, however, concerning small defects not requiring operation, and the correlation found does not appear sufficient in selecting patients for surgery. Chiotellis *et al.*[12] found a linear correlation ($r = 0.57$) between flow ratio and the ratio of the maximum opening of the two atrioventricular valves in 27 patients. Our high correlation coefficient of 0·80 may be explained by the systematic use of the maximum ratio comparing several transducer and patient positions. Still, the correlation does not appear adequate for definitive shunt evaluation. It should be realised that an increased T/M ratio does not necessarily express an increased flow ratio, but may merely reflect right heart enlargement and facilitate visualisation of parts of the tricuspid valve not seen in normal subjects.

The considerable variation in type of septal motion within the same patient is noteworthy. This finding has been described by Kerber *et al.*[18] in occasional patients, but appears from our series to be a common feature in patients with atrial septal defect; the degree of variation is probably dependant on the number of projections available.

Conclusion

Given an auscultatory and electrocardiographic suspicion of uncomplicated atrial septal defect, the combined finding of a normal chest *x*-ray film and a normal M-mode echocardiogram appears to indicate that there is no atrial septal defect. Phonocardiography seems to be of less value in excluding atrial septal defect.

Confirmation of an atrial septal defect was correctly obtained by echocardiography in all our cases and no false positive diagnosis was made either by radiological examination or by phonocardiography. Our data on small atrial septal defects with left-to-right shunts below the operative range are too limited to draw definite conclusions. It appears that a patient with echocardiographic findings of right ventricular volume overload, A_2P_2 variation below 15 ms during normal respiration, and a chest *x*-ray suggesting a large left-to-right shunt will, at right heart catheterisation, demonstrate the need for closing an atrial septal defect.

In our series of 23 patients with a clinical suspicion of atrial septal defect all six patients without defects were correctly excluded by chest *x*-ray and echocardiography. Six patients with atrial septal defect diagnosed by chest *x*-ray and echocardiography with a phonocardiographic confirmation in four cases were correctly selected for operation based on radiological findings. Thus, a total of 12 out of 23 patients (52%: 95% confidence limits 31 to 73%) appears to be definitely evaluated without heart catheterisation.

Improved non-invasive diagnostic results can perhaps be provided in the future using techniques such as radionuclide examinations and by developing ultrasonic methods.

References

1 Bahler AS, Meller J, Brik H, Herman MV, Teichholz LE. Paradoxical motion of the interventricular septum with right ventricular dilatation in the absence of shunting. *Am J Cardiol* 1976; **38:** 654–7.

2 Fraker TD Jr, Harris PJ, Behar VS, Kisslo JA. Detection and exclusion of interatrial shunts by two-dimensional echocardiography and peripheral venous injection. *Circulation* 1979; **59:** 379–84.

3 Weyman AE, Wann LS, Caldwell RL, Hurwitz RA, Dillon JC, Feigenbaum H. Negative contrast echocardiography. A new method for detecting left-to-right shunts. *Circulation* 1979; **59:** 498–505.

4 Kalmanson D, Veyrat G, Derai C, Savier CH, Berkman M, Chiche P. Non-invasive technique for diagnosing atrial septal defect and assessing shunt volume using directional Doppler ultrasound. *Br Heart J* 1972; **34:** 981–91.

5 Flaherty JT, Canent RV Jr, Boineau JP, Anderson PAW, Levin AR, Spach MS. The use of externally recorded radioisotope-dilution curves for quantitation of left-to-right shunts. *Am J Cardiol* 1967; **20:** 341–5.

6 Simon M. The pulmonary vasculature in congenital heart disease. *Radiol Clin North Am* 1968; **6:** 303–17.

7 Leatham A, Gray I. Auscultatory and phonocardiographic signs of atrial septal defect. *Br Heart J* 1956; **18:** 193–208.

8 Feigenbaum H. *Echocardiography*. 2nd ed. Philadelphia: Lea & Febiger, 1976.

9 Shafter HA. Splitting of the second heart sound. *Am J Cardiol* 1960; **6:** 1013–22.

10 Diamond MA, Dillon JC, Haine CL, Chang S, Feigenbaum H. Echocardiographic features of atrial septal defect. *Circulation* 1971; **43:** 129–35.

11 Radtke WE, Tajik AJ, Gau GT, Schattenberg TT, Guiliani ER, Tancredi RG. Atrial septal defect: echocardiographic observations. Studies in 120 patients. *Ann Intern Med* 1976; **84:** 246–53.

12 Chiotellis P, Lees R, Goldblatt A, Liberthson R, Myers G. New criteria for echocardiographic diagnosis of atrial septal defect (abstract). *Circulation* 1975; **51 & 52,** suppl II: 135.

13 Andersen M, Lyngborg K, Møller I, Wennevold A. The natural history of small atrial septal defects: long-term follow-up with serial heart catheterizations. *Am Heart J* 1976; **92:** 302–7.

14 Wennevold A. Hydrogen in the detection of minute left-to-right shunts. *Scand J Clin Lab Invest* 1966; **19:** 181–5.

15 Pearlman AS, Borer JS, Clark CE *et al.* Abnormal right ventricular size and ventricular septal motion after atrial septal closure. *Am J Cardiol* 1978; **41:** 295–301.

16 Tajik AJ, Gau GT, Schattenberg TT, Ritter DG. Normal ventricular septal motion in atrial septal defect. *Mayo Clin Proc* 1972; **47:** 635–8.

17 Tajik AJ, Gau GT, Schattenberg TT. Echocardiogram in atrial septal defect with small left-to-right shunt. *Chest* 1973; **63:** 95.

18 Kerber RE, Dippel WF, Abboud FM. Abnormal motion of the interventricular septum in right ventricular volume overload. *Circulation* 1973; **48:** 86–96.

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Estimation of pulmonary artery wedge pressure from chest radiograph in patients with chronic congestive cardiomyopathy and ischaemic cardiomyopathy*

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SUMMARY In order to define the relation between chest *x*-ray findings and the level of pulmonary artery wedge pressure in patients with chronic congestive cardiomyopathy, 82 patients had chest radiographs before undergoing 92 haemodynamic studies. The studies were divided into three groups according to the level of pulmonary artery wedge pressure (PAWP) (group 1: <15 mmHg, group 2: 15 to 24 mmHg, group 3: $\geqslant 25$ mmHg.

Venous distribution, interstitial oedema, pleural effusions, left atrial enlargement, and right ventricular enlargement each occurred in less than 10 per cent of group 1 studies. Radiological abnormalities generally distinguished group 1 from group 2, but none except cardiothoracic ratio distinguished group 2 from group 3. Cardiothoracic ratio correlated best with pulmonary artery wedge pressure ($r=0{\cdot}70$). Alveolar oedema was uncommon when PAWP $\geqslant 25$ mmHg, occurring in 32 per cent of group 3 studies.

Stepwise multiple linear regression analysis showed that cardiothoracic ratio, alveolar oedema, interstitial oedema, and left atrial size each contributed independently to the prediction of PAWP. The regression analysis improved the accuracy of the estimation of PAWP from the findings noted on standard chest radiographs.

A rise in left ventricular diastolic and pulmonary artery wedge pressures is a characteristic haemodynamic finding in patients with chronic congestive cardiomyopathy. However, the magnitude of the rise in pulmonary artery wedge pressure may vary widely in such patients; and, in a few, it may even be normal. Accurate determination of the level of pulmonary venous hypertension in these patients is useful for the choice of appropriate treatment, particularly for the choice of vasodilator agents which are now widely used for treatment of chronic congestive heart failure.[1–4] At present, invasive haemodynamic monitoring is most commonly used to assess the severity of pulmonary venous hypertension in these patients. An accurate noninvasive method for the prediction of pulmonary artery wedge pressure would thus be extremely useful in clinical practice.

The chest radiograph has been used to evaluate the haemodynamic status of patients with cardiac disease in the past.[5–11] However, much of the data derives from patients with rheumatic mitral valvular disease,[5–8 12–14] especially mitral stenosis, and it remains to be seen that the established radiological criteria for estimating pulmonary artery wedge pressure are applicable to patients with chronic left ventricular failure. The purpose of this study, therefore, was to assess the value of chest radiographic findings for the estimation of pulmonary artery wedge pressure in patients with chronic left ventricular failure.

Subjects and methods

All patients undergoing haemodynamic monitoring for symptoms of chronic congestive heart failure at

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the University of California, San Francisco, between January 1975 and January 1979, were evaluated for eligibility in the study. Patients were accepted into the study if they met the following criteria: (1) symptoms of heart failure of more than one month's duration; (2) a standard posteroanterior and lateral chest radiograph performed within 72 hours before haemodynamic evaluation; (3) a stable clinical status without change in symptomatology or therapeutic regimen during the interval between radiological and haemodynamic assessment. Patients with valvular or congenital heart disease or hypertrophic cardiomyopathy were excluded from the study. Of a total of 128 patients, 56 met the above criteria. Thirty-eight patients undergoing 46 haemodynamic studies were evaluated retrospectively. Eighteen patients undergoing 20 studies were then evaluated prospectively. An additional 26 patients without symptoms of heart failure who underwent right heart catheterisation during the course of evaluation for chest pain syndromes served as a control group. Twenty were evaluated retrospectively and six prospectively. Thus, the retrospective group consisted of 24 patients undergoing 26 haemodynamic studies.

All patients had chronic exertional dyspnoea of over one month's duration. Those who had biplane left ventricular angiography had an ejection fraction $\leqslant 0{\cdot}40$. All had, in addition, at least two of the following characteristics: (1) a third heart sound, (2) raised jugular venous pressure, (3) a sustained laterally displaced left ventricular impulse, (4) chronic digitalis or diuretic requirements, (5) pulmonary artery wedge pressure $\geqslant 15$ mmHg, (6) cardiac index $\leqslant 2{\cdot}2$ l/min per m^2. Fifty-three of the patients with congestive cardiomyopathy were in New York Heart Association class III or IV heart failure at the time of the study; three were in class II. Two of the patients in class IV had improved to class II at the time of their second study.

PATIENT POPULATION

The mean age of patients with cardiomyopathy was 59 ± 13 (± 1 SD) years compared with 55 ± 12 years for the patients in the control group. The difference was not statistically significant. The mean ages of the patients and controls in the retrospective and prospective groups were similar to the groups as a whole.

Both cardiomyopathy and control populations were predominantly male, with 39 (70%) men in the former and 21 (81%) men in the latter (NS). The sex ratios of the cardiomyopathy and control patients in the retrospective and prospective groups were also similar to those of the overall groups and not statistically different from one anotner.

Thirty-two (57%) of the heart failure patients had cardiomyopathy secondary to coronary artery disease, as determined by coronary angiography or a documented history of multiple myocardial infarctions (ischaemic cardiomyopathy). Three had alcoholic cardiomyopathy, one was diabetic with normal coronary arteries, and one was a female carrier for the X-linked disorder, Duchenne's muscular dystrophy. Thirteen (23%) had a congestive cardiomyopathy of undetermined aetiology. Because of similar clinical and haemodynamic presentations in patients with ischaemic cardiomyopathy and in patients with congestive cardiomyopathy, results were analysed together.

Of the control population, 21 had coronary artery disease and five had atypical chest pain with normal coronary arteries.

HAEMODYNAMIC EVALUATION

Right heart catheterisation with a Swan-Ganz catheter was performed in the cardiac catheterisation laboratory or the coronary care unit after the patients gave informed consent. Pulmonary artery and pulmonary artery wedge pressures were measured with the patient lying supine using a Statham P231d or P231a strain gauge. Zero reference level was at the mid-axillary line.

The patients evaluated retrospectively were divided into three groups according to their mean pulmonary artery wedge pressure: group 1 included those with pulmonary artery wedge pressure < 15 mmHg; group 2 included those with pulmonary artery wedge pressure 15 to 24 mmHg; and group 3 included those with pulmonary artery wedge pressure $\geqslant 25$ mmHg.

RADIOLOGICAL INDICES

All chest radiographs were obtained in the Radiology Department. Posteroanterior and lateral projections were obtained at end inspiration with an *x*-ray source-to-film distance of six feet at approximately 140 kV.

Cardiac size was evaluated using the cardiothoracic ratio, which was measured as the maximum transverse diameter of the heart divided by the maximum thoracic width.[15] In addition, the presence of left and right ventricular and left atrial chamber enlargement was recorded. Definitions of chamber enlargement were based on standard criteria.[15]

Pulmonary venous flow redistribution was defined as the presence of a disparity between the calibre of the upper and lower lobe pulmonary vessels with distention of the upper vessels.[10 12] Interstitial oedema was recognised as perivascular or peribronchial cuffing, or Kerley's septal lines.[16] Alveolar oedema was diagnosed as a hazy mottling of small more discrete densities, some confluent, without the linear appearance characteristics of interstitial oedema, and with poorly defined borders.[7 17] Pleural effusions were noted. Pulmonary venous flow redistribution, interstitial oedema, alveolar oedema, and pleural effusion were termed as "fluid abnormalities".

Finally, the presence or absence of hilar and pulmonary artery enlargement was recorded.[6]

Chest radiographs were interpreted by one observer without knowledge of the clinical or haemodynamic status of the patients. To assess intraobserver variability, 20 chest radiographs were reinterpreted blindly three months after initial radiological assessment.

STATISTICAL ANALYSIS

The data were processed using the statistical packages provided by the BMDP Biomedical Computer Programs P-series.[18] Comparisons of groups of data consisting of continuous variables (as in Table 1 and Fig. 1) were done with t tests or analysis of variance followed by a Student-Newman-Keuls multiple comparison test. Groups of discrete variable (see Fig. 2 and 3) were evaluated with non-parametric statistics, including the Mann-Whitney and Kruskal-Wallis tests.

Table *Haemodynamic results*

Group	*PAWP (mmHg)*		*PAP (mmHg)*	
1 (N=25)	9·4 ±2·6*	p < 0·001	15·6 ±2·6	p < 0·001
2 (2 (N=13)	19·7 ±3·2		30·0 ±6·0	
3 (N=28)	30·8 ±4·5	p < 0·001	40·4 ±6·0	p < 0·001

* Mean ±1 SD.
Abbreviations: PAWP = pulmonary artery wedge pressure; PAP = pulmonary artery pressure; N = number of studies; 1 = studies with PAWP < 15; 2 = studies with PAWP 15 to 24; 3 = studies with PAWP ≥25.

Bivariate linear regression and stepwise multiple linear regression analysis were also used to relate the radiological data to the haemodynamics (Fig. 4). The stepwise regression program evaluated all the variables presented to it and selected only those radiological variables which contributed independently to a significant degree to the prediction of pulmonary artery wedge pressure. Multiple correlation coefficients (r), fraction of variance explained (R^2), levels of significance for each variable and the overall regression, and standardised regression coefficients were obtained at each step. The latter are normalised values which take into account the different units and variances of the variables.

Results

INTRAOBSERVER VARIABILITY

Analysis of intraobserver variability showed that interpretation of the chest radiographs was highly consistent, except for the assessment of hilar and pulmonary artery size. The initial mean cardiothoracic ratio of the 20 radiographs read twice was 0·58±0·11 (± 1SD) and the subsequent value 0·58±0·10. All paired cardiothoracic ratios were consistent to 2 per cent except two pairs which were accurate to 6 and 5 per cent of one another. Paired

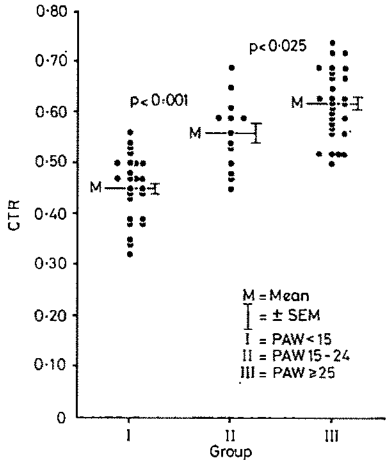


Fig. 1 *Plotted are the means and individual values for the cardiothoracic ratios in each group of patients. The mean value of group 2 was significantly higher ($p < 0·001$) than group 1, and that of group 3 significantly higher than group 2 ($p < 0·025$).*

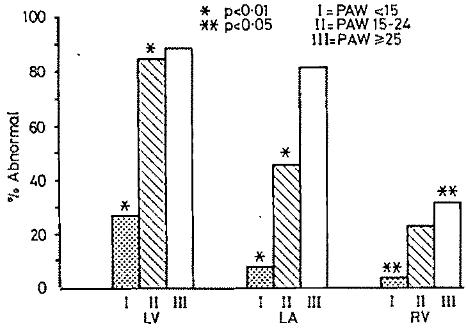


Fig. 2 *Presented are histograms showing the percentage of findings with left ventricular (LV) enlargement, left atrial (LA) enlargement, and right ventricular (RV) enlargement in each group.*

estimates of the pulmonary venous pattern, presence of interstitial and alveolar oedema, pleural effusions, left and right ventricular size, and left atrial size were all consistent in at least 90 per cent of cases. On the other hand, 20 per cent of estimates of pulmonary artery size and 40 per cent of estimates of hilar size were inconsistent. Given the high variability in the assessment of pulmonary artery and hilar size, these two radiological variables were excluded from the analysis relating the chest radiographic findings to pulmonary artery wedge pressure. All the other chest *x*-ray indices described above form the bases for the subsequent results.

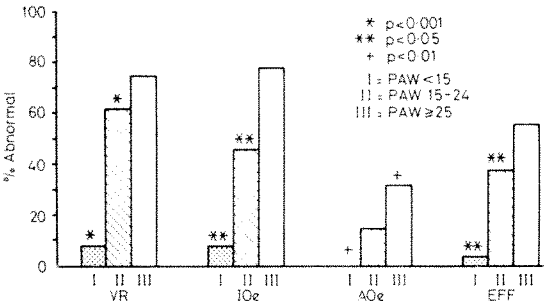


Fig. 3 *Presented are histograms showing the percentage of findings with venous redistribution (VR), interstitial oedema (IOe), alveolar oedema (AOe), and pleural effusions (EFF) in each group.*

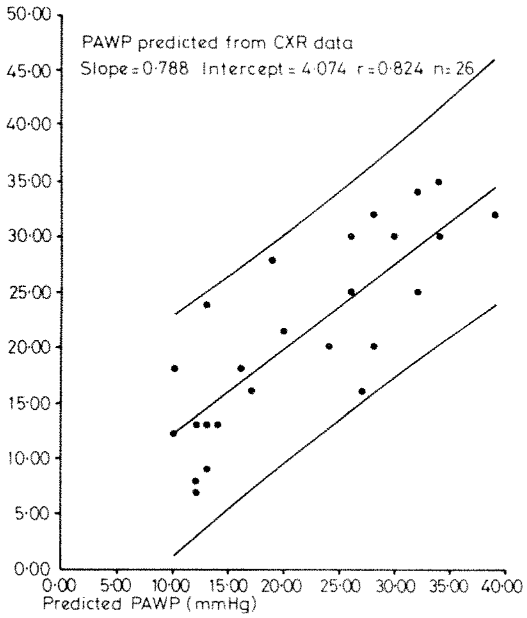


Fig. 4 *Plotted is the predicted versus the observed pulmonary artery wedge pressures in the prospective group of studies, the resultant linear regression formula (slope = 0·79, r = 0·82), and the 95 per cent confidence limits.*

Retrospective results

HAEMODYNAMIC FINDINGS

Of the 66 studies done retrospectively, the mean pulmonary artery wedge pressure was 26·0 ± 8·2 (± 1 SD) mmHg for the cardiomyopathy group and 9·1 ± 2·5 mmHg for the control population (p < 0·001). The Table lists the resultant mean pulmonary artery wedge and pulmonary artery pressures after the patients and controls were divided into three groups according to their pulmonary artery wedge pressure. It is, therefore, not surprising that the haemodynamics of each group were highly statistically different (p < 0·001) group 1 vs. 2, and 2 vs. 3 for pulmonary artery wedge and pulmonary artery pressures.

RADIOLOGICAL ASSESSMENT OF CARDIAC ENLARGEMENT AND CHAMBER SIZE

Heart size alone, as estimated by cardiothoracic ratio, correlated well with pulmonary artery wedge pressure (r = 0·70). However, the 95 per cent confidence limits were wide, making the prediction of an individual patient's pulmonary artery wedge pressure somewhat uncertain. This difficulty is illustrated in Fig. 1, in which the cardiothoracic ratios for all the retrospective studies are plotted according to group. Mean cardiothoracic ratio for the group 1 patients was 0·45 ± 0·06; for the group 2 patients, 0·57 ± 0·08; and for the group 3 patients, 0·62 ± 0·08 (p < 0·001 1 vs. 2, p < 0·025 2 vs. 3). It can be seen, however, that the overlap among the groups is great enough to make the classification of individual patients difficult. Generally, a cardiothoracic ratio ≥0·60 was predictive of pulmonary artery wedge pressure ≥25 mmHg; 77 per cent of studies with a cardiothoracic ratio ≥0·60 occurred when pulmonary artery wedge pressure was ≥25 mmHg. On the other hand, the sensitivity of such an abnormal cardiothoracic ratio for a pulmonary artery wedge pressure ≥25 mmHg was low, occurring in 58 per cent of the group 3 patients. Normal cardiothoracic ratio (≤0·50) suggested normal pulmonary venous pressure; 88 per cent of studies with cardiothoracic ratio ≤0·50 had pulmonary artery wedge pressure < 15 mmHg. Only 68 per cent of all studies, however, with pulmonary artery wedge pressure < 15 mmHg had a normal cardiothoracic ratio.

Fig. 2 depicts the presence of chamber enlargement in the three groups. Left ventricular enlargement occurred in 27 per cent of group 1 patients, whereas left atrial or right ventricular enlargement occurred in less than 10 per cent of group 1 patients. Though left ventricular and left atrial enlargement were statistically more frequent when pulmonary artery wedge pressure was raised ($p < 0{\cdot}01$), no chamber assessment discriminated those with mild to moderate (group 2) from those with severe (group 3) rises in pulmonary artery wedge pressure.

Fig. 3 shows the presence of "fluid abnormalities" in the three groups. Fluid abnormalities were uncommon when pulmonary artery wedge pressure was 15 mmHg. Venous redistribution, interstitial oedema, and pleural effusions occurred in less than 10 per cent of group 1 patients, while alveolar oedema occurred in none. Venous abnormalities ($p < 0{\cdot}001$), interstitial oedema ($p < 0{\cdot}05$), and pleural effusions ($p < 0{\cdot}05$) all distinguished group 1 from group 2. None of the radiological types of fluid abnormalities, however, were statistically more frequent when the group 3 studies were compared with those in group 2. Alveolar oedema was present rarely even when pulmonary capillary wedge pressure was >25 mmHg, when it was present in 32 per cent of studies.

Multiple linear regression analysis showed that radiological assessment of cardiothoracic ratio, alveolar oedema, interstitial oedema, and left atrial size (in that order of importance) all independently contributed to the estimation of pulmonary artery wedge pressure $r = 0{\cdot}82$). Cardiothoracic ratio accounted for 48 per cent of the variance explained (R^2); alveolar oedema 11 per cent, and interstitial oedema and left atrial size, each 4 per cent. The standardised regression coefficients of each variable were similar, however, indicating that all four variables were important for the estimation of pulmonary artery wedge pressure from the chest radiograph. The regression formula was:

$$\begin{aligned} \text{PAWP} = &-2{\cdot}6 \pm 21{\cdot}1\ (\text{CTR}) + 5{\cdot}5\ (\text{AOe}) \\ &+ 5{\cdot}4\ (\text{IOe}) + 6{\cdot}3\ (\text{LA}) \end{aligned}$$

where PAWP = pulmonary artery wedge pressure and is measured in mmHg, CTR = cardiothoracic ratio, AOe = alveolar oedema, IOe = interstitial oedema, and LA = left atrial enlargement. AOe, IOe, or LA were given a value of "1" if the particular abnormality was present and "0" if absent.

Prospective results

In order to test the validity of the derived stepwise linear regression formula, the formula was then applied to the radiological data of the studies obtained prospectively. The formula was used to derive predicted pulmonary artery wedge pressures from the prospective radiological data. The predicted pressures were then correlated with actual pressures. The results are plotted in Fig. 4. The correlation is excellent, with $r = 0{\cdot}82$, a value similar to that obtained from the retrospective data.

Discussion

Previous investigations documented the value of the chest radiographic findings of pulmonary venous flow redistribution, interstitial oedema, alveolar oedema, and pulmonary arterial enlargement in the noninvasive estimation of the haemodynamics in patients with rheumatic mitral valvular disease.[5 7 8 12–14 19 20] Indeed, Milne[13] synthesised the available data and presented specific radiological criteria for the estimation of both mean pulmonary artery and pulmonary artery wedge pressures in patients with mitral stenosis.

In the present study an attempt was made to evaluate the predictive value of various radiological findings for the estimation of pulmonary venous pressure in patients with chronic congestive heart failure who did not have valvular heart disease. Our findings document that the presence of most chest radiographic abnormalities in patients with chronic congestive cardiomyopathy and ischaemic cardiomyopathy indicates raised pulmonary artery wedge pressure (Fig. 1 to 3). Alveolar oedema was conspicuously absent in patients with normal pulmonary artery wedge pressure. Left atrial and right ventricular enlargement also occurred rarely ($<10\%$) when pulmonary venous pressure was normal. The only radiological abnormality common despite a normal pulmonary artery wedge pressure was left ventricular enlargement (27% of group 1 studies). This finding may reflect the nature of our control patients: many had prior myocardial infarction and/or hypertension.

Our observations in patients with chronic congestive cardiomyopathy are at variance with those in patients with acute heart failure secondary to myocardial infarction as reported by Kostuk *et al.*[21] who showed that in the setting of acute myocardial infarction, the chest radiograph predicted accurately the pulmonary artery wedge pressure in only 43 per cent of patients, underestimated it in 24 per cent, and overestimated it in 33 per cent. We found that radiographic analysis in chronic heart failure rarely overestimated pulmonary artery wedge pressure. Rapidly changing haemodynamics in patients with acute myocardial infarction may account for this discrepant result.

Although the presence of "fluid abnormalities" in patients with chronic congestive heart failure in our study was useful to separate patients with normal pulmonary artery wedge pressure from those with raised pulmonary artery wedge pressure, the findings did not help in distinguishing patients with moderate increases in pulmonary artery wedge pressure (group 2) from those with severe increases (group 3) (Fig. 2). Our findings differ from those of Turner *et al.*[11] who estimated pulmonary haemodynamics from the chest radiographic analysis of fluid abnormalities and pulmonary arterial size. However, in their study haemodynamic and radiological correlations are not presented other than several individual cases, and the patient population is not identified. Moreover, in our study we have shown, as have others previously,[9] that the radiological estimation of pulmonary size may be in error.

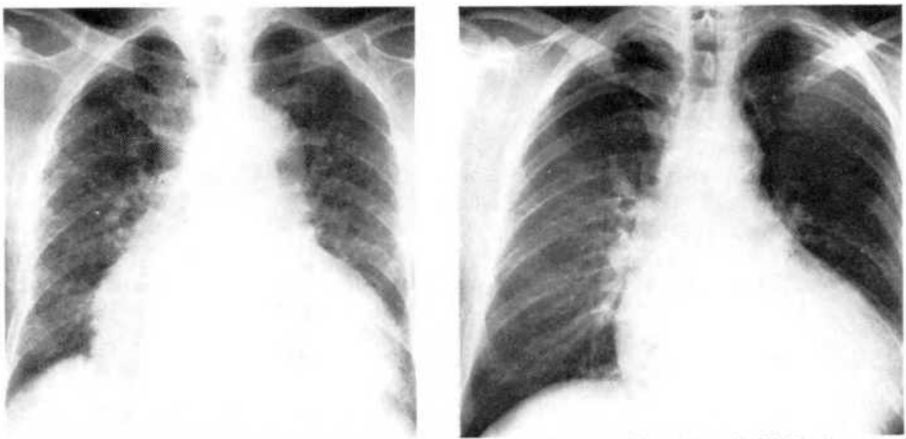
Of the fluid abnormalities, alveolar oedema was the most specific predictor of a raised pulmonary artery wedge pressure in our study. No group 1 patient had alveolar oedema. Yet alveolar oedema was also uncommon, despite severe increases in pulmonary artery wedge pressure.[18] Some authors[11 15] have suggested that transudation of oedema into the alveoli does not occur until the pulmonary artery wedge pressure reaches 30 to 35 mmHg. Of our studies in which pulmonary artery wedge pressure was at least 30 mmHg, alveolar oedema was present in 30 per cent. One possible explanation for infrequent pulmonary oedema despite severe rises in pulmonary venous pressure is that, during chronic heart failure, lymphatic hypertrophy and hyperplasia and changes in the pulmonary interstitium allow for a more efficient removal of oedema from the lungs than in acute heart failure.[22]

Cardiomegaly as assessed by cardiothoracic ratio proved to be the single most important predictor of pulmonary artery wedge pressure in our study (Fig. 1). This finding, however, is contrary to the data reported in the setting of acute myocardial infarction by McHugh *et al.*[23] and Kostuk *et al.*[21] The different findings may relate to cardiovascular adaptation to heart failure. Gradual left ventricular dilatation is the usual pathophysiological response to an increase in left ventricular filling pressure and a reduction in myocardial contractility.[24] Consequently, cardiomegaly is more likely to be present in chronic rather than acute left ventricular failure. In fact, Kostuk *et al.*[21] noted that those patients with radiographic cardiomegaly nearly always had raised pulmonary capillary wedge pressure.

Our data are in agreement with those of Harlan *et al.*[25] who found that radiological estimate of heart volume was the most important clinical descriptor of a group of patients with ischaemic cardiomyopathy. Though Yatteau *et al.*[26] found normal heart size in 27 per cent of their patients with ischaemic cardiomyopathy, 60 per cent of their patients were in New York Heart Association class I or II heart failure, whereas only 6 per cent of our patients were in class I or II.

Although in the present study cardiothoracic ratio correlated best with pulmonary artery wedge pressure (r = 0·70), the accuracy of the ratio in predicting the level of increase in pulmonary artery wedge pressure in individual patients was low. In many patients the cardiothoracic ratio could not be used to estimate the pulmonary artery wedge pressure with enough precision to be clinically useful.

The present study indicates that a combination of radiological variables might more accurately predict the level of pulmonary artery wedge pressure. The stepwise multiple linear regression formula, using the variables cardiothoracic ratio, alveolar oedema, interstitial oedema, and left atrial size, predicted pulmonary capillary wedge pressure fairly accurately in patients with ischaemic as well as congestive cardiomyopathy (r = 0·82). The regression equation derived from the retrospective data was used prospectively to estimate pulmonary artery wedge pressure in 26 studies, and a close estimation of pulmonary artery wedge pressure was possible in most patients (r = 0·82). It needs to be emphasised, however, that the slope of the regression line in the prospective evaluation was 0·79, indicating that the radiological findings tended to underestimate the pulmonary artery wedge pressure to some extent (Fig. 4). This is not surprising given that alveolar oedema occurred infrequently, yet was the second most important predictor for raised pulmonary artery wedge pressure in our study. Fig. 5 illustrates the difficulty that exists in the radiological estimation of the pulmonary haemodynamics in patients with chronic congestive cardiomyopathy. The two patients whose *x*-rays are shown in Fig. 5 both had identical haemodynamic findings with cardiac indices of 1·5 l/min per m^2 and pulmonary artery wedge pressure of 32 mmHg. Both patients had gross cardiomegaly and left ventricular and atrial enlargement, yet only the patient in Fig. 5A had pulmonary venous flow redistribution, interstitial oedema, and alveolar oedema. Using traditional criteria, a radiologist might estimate that the patient in Fig. 5B had normal or minimally raised left ventricular filling pressures; using the stepwise linear regression formula, the estimated pulmonary artery wedge pressure is 23 mmHg, and slightly



PT060 PCW: 32 mmHg CI: 1·4 l/min per m2
A

PT 069 PCW: 32mmHg CI: 1·5 l/min per m2
B

Fig. 5 *Shown are chest radiographs from two patients with identical haemodynamics (pulmonary artery wedge pressure = 32 mmHg and cardiac index = 1·5 l/min per m²) and different radiographic findings.*

underestimates the true pulmonary artery wedge pressure, though it is still grossly abnormal.

In conclusion, our study has shown that, though chest radiographic abnormalities are helpful to identify the presence of raised pulmonary venous pressure in patients with ischaemic and congestive cardiomyopathy, the prediction of the level of pulmonary venous pressure from any single radiological variable is not possible. Multiple stepwise linear regression analysis improves the predictive value of the radiological variables for the estimation of pulmonary artery wedge pressure. A prospective study involving a much larger group of patients will be needed to evaluate further the value of the regression analysis for the estimation of pulmonary artery wedge pressure in these patients.

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References

1 Kovick RB, Tillisch JH, Berens SC, Bramowitz AD, Shine KI. Vasodilator therapy for chronic left ventricular failure. *Circulation* 1976; **53:** 322–8.

2 Franciosa JA, Mikulic E, Cohn JN, Jose E, Fabi A. Hemodynamic effects of orally administered isosorbide dinitrate in patients with congestive heart failure. *Circulation* 1974; **50:** 1020–4.

3 Chatterjee K, Parmley WW, Massie B, *et al*. Oral hydralazine therapy for chronic refractory heart failure. *Circulation* 1976; **54:** 879–83.

4 Chatterjee K, Drew D, Parmley WW, Klausner SC, Polansky J, Zacherle B. Combination vasodilator therapy for severe chronic congestive heart failure. *Ann Intern Med* 1976; **85:** 467–70.

5 Grainger RC. Interstitial pulmonary oedema and its radiological diagnosis: a sign of pulmonary venous and capillary hypertension. *Br J Radiol* 1958; **31:** 201–17.

6 Lavender JP, Doppman J. The hilum in pulmonary venous hypertension. *Br J Radiol* 1962; **35:** 303–13.

7 Steiner RE. Radiology of pulmonary circulation. *Am J Roentgenol* 1964; **91:** 249–64.

8 Simon M, Sasahara AA, Cannilla JE. The radiology of pulmonary hypertension. *Semin Roentgenol* 1967; **2:** 368–88.

9 Short DS. Radiology of the lung in left heart failure. *Br Heart J* 1956; **18:** 233–40.

10 Simon M. The pulmonary vessels in incipient left ventricular decompensation. *Circulation* 1961; **24:** 185–90.

11 Turner AF, Lau FYK, Jacobson G. A method for the estimation of pulmonary venous and arterial pressures from the routine chest roentgenogram. *Am J Roentgenol* 1972; **116:** 97–106.

12 Simon M. The pulmonary veins in mitral stenosis. *J Fac Radiologists* 1956; **9:** 25–32.

13 Milne ENC. Physiological interpretation of the plain radiograph in mitral stenosis, including a review of criteria for the radiological estimation of pulmonary arterial and venous pressures. *Br J Radiol* 1963; **36:** 902–13.

14 Chen JTT, Behar VS, Morris JJ Jr, McIntosh HD, Lester RG. Correlation of roentgen findings with hemodynamic data in pure mitral stenosis. *Am J Roentgenol* 1968; **102:** 280–92.

15 Jefferson K Rees S. *Clinical cardiac radiology*. London: Butterworth, 1973: 3–25, 84–94.
16 Chait A. Interstitial pulmonary edema. *Circulation* 1972; **45:** 1323–30.
17 Meszaros WT. Lung changes in left heart failure. *Circulation* 1973; **47:** 859–71.
18 Dixon WJ, Brown MB, eds. *BMDP-77, Biomedical computer programs, P-series*. Rev. ed. Berkeley: University of California Press, 1978: 1–154, 167–98, 375–417.
19 Lavender JP, Doppman J, Shawdon H, Steiner RE. Pulmonary veins in left ventricular failure and mitral stenosis. *Br J Radiol* 1962; **35:** 293–302.
20 Salzmann C, Sutton GC, Chatterjee K, Kerr IH, Miller GAH. Assessment of homograft replacement of mitral valve by chest radiographs. *Br Heart J* 1972; **34:** 121–8.
21 Kostuk W, Barr JW, Simon AL, Ross J Jr. Correlations between the chest film and hemodynamics in acute myocardial infarction. *Circulation* 1973; **48:** 624–32.
22 Harris P, Heath D. *The human pulmonary circulation* 2nd ed. Edinburgh: Churchill Livingstone, 1977: 341–3, 361–2.
23 McHugh TJ, Forrester JS, Adler L, Zion D, Swan HJC. Pulmonary vascular congestion in acute myocardial infarction: hemodynamic and radiologic correlations. *Ann Intern Med* 1972; **76:** 29–33.
24 Mason DT, Spann JF Jr, Zelis R, Amsterdam EA. Alterations of hemodynamics and myocardial mechanics in patients with congestive heart failure: pathophysiologic mechanisms and assessment of cardiac function and ventricular contractility. *Prog Cardiovasc Dis* 1970; **12:** 507–57.
25 Harlan WR, Oberman A, Grimm R, Rosati RA. Chronic congestive heart failure in coronary artery disease: clinical criteria. *Ann Intern Med* 1977; **86:** 133–8.
26 Yatteau RF, Peter RH, Behar VS, Bartel AG, Rosati RA, Kong Y. Ischemic cardiomyopathy: the myopathy of coronary artery disease. *Am J Cardiol* 1974; **34:** 520–5.

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Prenylamine-induced ventricular tachycardia and syncope controlled by ventricular pacing

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SUMMARY We describe eight patients treated for angina with prenylamine who developed life-threatening ventricular arrhythmias after QT interval prolongation. When prenylamine administration was stopped QT interval shortened to within normal values, while the ventricular arrhythmias were controlled by a temporary ventricular pacemaker and disappeared after several days. We stress the importance of surveillance of the QT interval and ventricular arrhythmias in patients receiving long-term treatment with prenylamine.

Since its introduction as an antianginal agent, prenylamine has been shown to have a wide margin of therapeutic safety.[1] Indeed very few life-threatening complications of prenylamine treatment have been reported.[2–5] Thus the association of ventricular arrhythmias with prenylamine is of some interest, especially in view of the fact that it can be anticipated and thus avoided.

We report on the mode of treatment of eight patients with prolonged QT intervals and serious symptomatic ventricular tachyarrhythmias caused by prenylamine.

Patients and results

The eight patients constituting this group were admitted to the Department of Cardiology at the Lady Davis Carmel Hospital because of several episodes of syncope in the few weeks preceding admission.

They had coronary artery disease with mild anginal syndrome and were on a regimen of prenylamine 180 to 240 mg/day for at least two months before being admitted to hospital. Clinical details and additional drugs are summarised in the Table.

On arrival all patients had electrocardiograms showing prolonged QT interval, ventricular premature beats, and short runs of ventricular tachycardia with torsade de pointes pattern (Fig. 1–4).

In the first four patients treatment with lignocaine was initiated immediately; this failed, however, to control the arrhythmia. Moreover, two patients (cases 1 and 3) developed transient Mobitz second and third degree atrioventricular block on being given a 100 mg bolus of intravenous ligno-

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Table *Clinical, laboratory, and electrocardiographic data of patients on prenylamine with torsade de pointes*

Case no.	Age (y)	Sex	Additional drugs			No. of syncopalattacks		Duration of symptoms (wk)	Heart rate on admission	QT interval (s)	QTc on admission (s)	QTc on discharge (s)	Serum electrolytes (mg/100 ml)		
			Digoxin (mg)	Nitrites	Frusemide (mg)	Before admission	During hospital						mg	ca	K
1	76	F		+	—	6	1	8	40	0·58	0·61	0·37	2·3	9·1	4·9
2	62	F	—	+	40	2	—	4	60	0·70	0·78	0·42	1·8	9·0	4·0
3	82	M	0·25	+	—	> 10	5	8	58	0·64	0·64	0·32	1·9	11·3	4·0
4	72	F	—	+	40	3	1	5	54	0·60	0·57	0·36	2·2	11·7	5·3
5	67	F		+	—	4	—	10	61	0·66	0·66	0·41	2·1	9·0	4·6
6	64	M	—	+	—	2	—	3	53	0·60	0·56	0·42	2·2	10·7	5·1
7	74	F		+	—	1	—	1	56	0·52	0·50	0·39	2·0	10·1	4·7
8	84	F	—	+	80	7	2	13	71	0·64	0·70	0·43	1·9	9·0	3·9

QTc was calculated according to the formula of Bazzet: $\mathrm{QTc} = \dfrac{\mathrm{QT}}{\sqrt{\mathrm{R-R}}}$

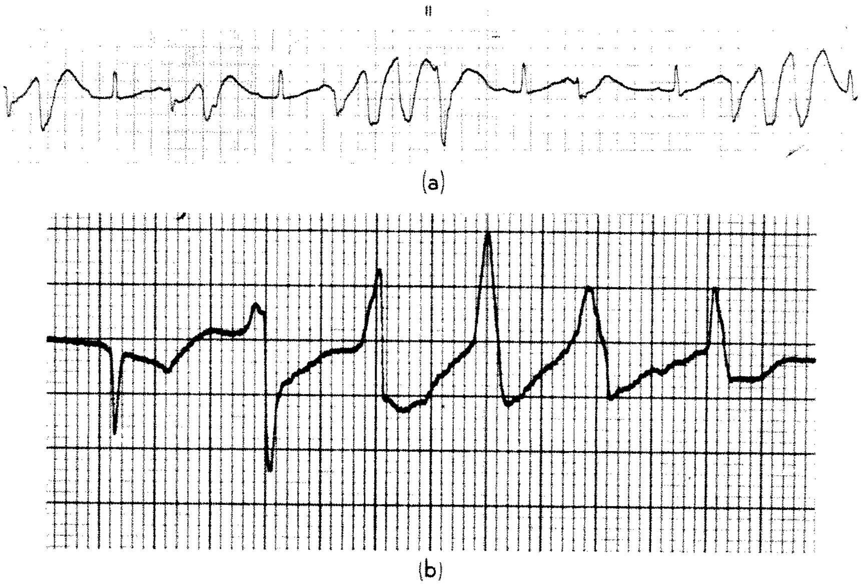
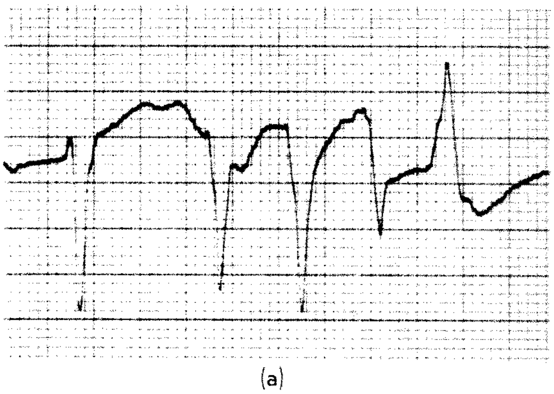
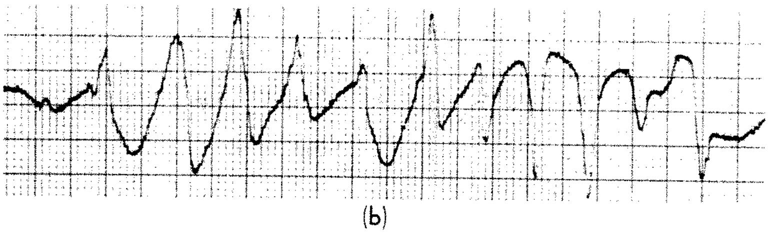


Fig. 1 (a) *Ventricular tachycardia showing torsade de pointes (lead II, case 1).* (b) *Ventricular tachycardia showing torsade de pointes (lead V1, case 1).*

Fig. 2 (a) *Ventricular tachycardia showing torsade de pointes (lead II, case 4).* (b) *Ventricular tachycardia showing torsade de pointes (praecordial lead V1, case 4).*





caine (Fig. 5). These four patients were treated by rapid ventricular pacing (100 pulses per minute) which proved to be effective in suppressing the ventricular arrhythmia. In view of the failure of lignocaine to control the arrhythmia and also the development of atrioventricular block in two patients, we treated the following four patients presenting to us by rapid ventricular pacing without attempting to initiate treatment with lignocaine. The arrhythmia was controlled successfully by this treatment.

The prolonged QT intervals returned to normal

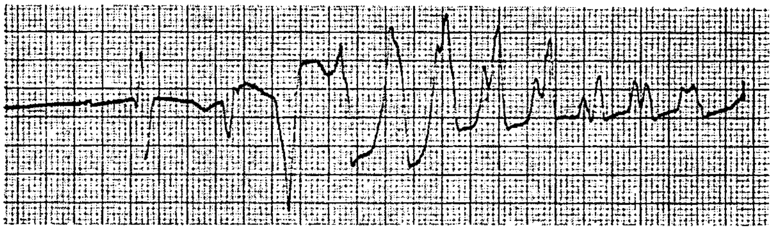


Fig. 3 *Ventricular tachycardia showing torsade de pointes (praecordial lead V1, case 3).*

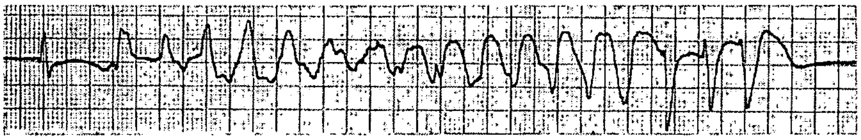


Fig. 4 *Ventricular tachycardia showing torsade de pointes (monitor lead, case 8).*

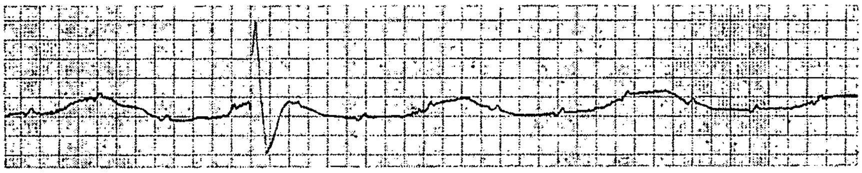


Fig. 5 *Complete atrioventricular block after 100 mg intravenous bolus of lignocaine. Thirteen P waves with one ventricular escape beat (praecordial lead V1, case 3).*

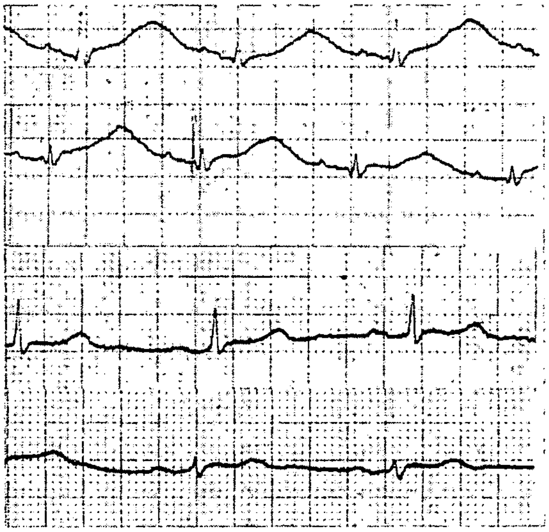


Fig. 6 *Prolonged QT interval 0·64 s (QTc=0·7) on admission and after a few days (lead aVL, case 8).*

values in all eight patients with concomitant cessation of the ventricular arrhythmias two to four days after prenylamine was discontinued (Fig. 6).

On admission none of these patients had clinical, electrocardiographic, or enzymatic signs of myocardial ischaemia or infarction. Serum potassium, magnesium, and calcium (Table) were within the normal range of values.

In addition, all the first and second degree relatives of our patients were examined and none was found to have prolongation of the QT interval on the electrocardiogram or a history of syncope.

Comment

Much is known about the pharmacological action of prenylamine[6] but the exact mechanism of its antianginal action is still uncertain. It seems probable that this is largely a result of inhibition of cathecholamine uptake by the storage granules.[7] It is known that intravenous prenylamine produces coronary vasodilatation and an increase in coronary blood flow.[8] Prenylamine is also known to delay calcium transport in the sarcoplasmic reticulum[9] and its antianginal effect is caused in part by its effect on electromechanical coupling. It is known to have a large number of side effects including sedation, gastrointestinal symptoms, and skin reactions.[10] Recently, a new complication has been described,[2-4] which includes prolongation of the QT interval and ventricular tachycardia with syncopal attacks.

QT prolongation may be a result of ischaemic heart disease,[11] hypokalaemia, hypocalcaemia,[12] hypomagnesaemia,[13] several antiarrhythmic drugs,[14] treatment with phenothiazines[15, 16] and tricyclic compounds,[16] liquid protein diets,[17] and is a feature of the Jervell-Lange-Nielson[18, 19] and the Romano-Ward syndromes.[20, 21] QT prolongation encourages re-entry processes and ventricular arrhythmias including torsade de pointes. Torsade de pointes may also arise during slow heart rhythm as an escape mechanism in sinus node dysfunction and atrioventricular block.[22, 23] It has also been reported in a neonate with myocarditis[24] and as a rare complication of ventricular pacing.[25]

In the eight cases described above we wish to draw attention to the prolongation of the QT interval induced by prenylamine, which was followed by torsade de pointes. The effects were reversible and controlled by ventricular pacing. All eight patients were examined echocardiographically and phonocardiographically and none was found to have prolapse of the mitral valve or any cardiomyopathy detectable by these tests. In all cases the prolonged QT intervals returned to normal values within several days after withdrawal of prenylamine, with the concomitant disappearance of the ventricular arrhythmias. Neither syncope nor palpitation has recurred in any of our patients on follow-up, and none has shown conduction disorders or arrhythmias.

The occurrence of atrioventricular block after an intravenous bolus of lignocaine is of some interest. The drug normally asserts minimal effects on the cardiac conducting system, and heart block induced by lignocaine is a rare complication.[26] Thus the induction of atrioventricular block in two patients of four to whom lignocaine was given is a source of some misgiving. Though unconfirmed, we cannot discount the possibility that at least in some cases lignocaine may be inadvisable in torsade de pointes.

The confident diagnosis of torsade de pointes requires the simultaneous recording of three leads; not every run of ventricular extrasystoles which change shape can be given this label. In view of the urgency of the situation we recorded only two leads (Fig. 1 and 2).

Torsade de pointes can be treated either by intravenous isoprenaline infusion or by pacing. Since the aetiology of the arrhythmia in our patients was secondary to prenylamine and there was a presumed risk of recurrence until serum levels of the drug would have fallen, we chose pacing, wishing to avoid the possible hazards of prolonged or repeated intravenous isoprenaline, especially in patients with angina.

We advise routine electrocardiographic observations in patients on prenylamine. Particular attention should be paid to the appearance of new albeit mild ventricular arrhythmias and prolongation of the QT interval, which may be the harbingers of life-threatening torsade de pointes.

References

1 Tucker H, Carson P, Bass N, Massey J. Prenylamine in treatment of angina. *Br Heart J* 1974; **36:** 1001–4.
2 Picard R, Auzepy P, Chauvin JP. Syncopes et altérations électrocardiographiques provoquées par la prénylamine. *Ann Cardiol Angeio (Paris)* 1971; **20:** 627–30.
3 Puritz R, Henderson MA, Baker SN, Chamberlain DA. Ventricular arrhythmias caused by prenylamine. *Br Med J* 1977; **ii:** 608–9.
4 Fazzini PF, Marchi F, Pucci P. Q-T lungo, sincope e prenilamina. *G Ital Cardiol* 1973; **3:** 233–9.
5 Fazzini PF, Marchi F, Pucci P. Ventricular tachycardia, a new iatrogenic possibility. *Am Heart J* 1975; **90:** 805–6.
6 Biochemical aspects of prenylamine. Proceedings of Symposium Capri. *Biochim Applicata* 1967; **14,** suppl 1.
7 Carlsson A, Waldeck B. On the mechanisms of action of prenylamine on tissue monamines. *Biochim Applicata* 1968; **14,** suppl 1: 41.
8 Ito Y, Hasegawa Y. The effect of coronary vasodilators on the coronary circulation and the myocardial metabolism in the sclerotic heart diseases. *Jpn Circ J* 1963; **27:** 164–71.
9 Schöne HH, Linder E. Die Wirkung des N-3'phenyl-propyl-(2')-1, 1 diphenyl-propyl-(3)-amins auf den Stoffwechsel Von Serotonin und Noradrenalin. *Arzneim Forsch* 1960; **10:** 583–5.
10 Stoker JB. Effect of prenylamine in angina pectoris. *Br J Clin Pract* 1968; **22:** 384–5.
11 Schamroth L. *Introduction to electrocardiography*. 4th ed. London: Blackwell Scientific Publications, 1971: 193.
12 Friedberg CK. *Diseases of the heart*. 3rd ed. London: Saunders, 1966: 1660.
13 Loeb HA, Pietras RJ, Gunnar RM, Tobin JR Jr. Paroxysmal ventricular fibrillation in two patients with hypomagnesemia: treatment by transvenous pacing. *Circulation* 1968; **37:** 210–5.
14 Goodman LS, Gilman A. *The pharmacological basis of therapeutics*. 5th ed. New York: Macmillan, 1975: 683–91.
15 Shoonmaker FW, Osteen RT, Greenfield JC Jr. Thioridazine (Mellaril) induced ventricular tachycardia controlled with an artificial pacemaker. *Ann Intern Med* 1966; **65:** 1076–8.
16 Fowler NO. McCall D, Chou TC, Holmes JC, Hanenson IB. Electrocardiographic changes and cardiac arrhythmias in patients receiving psychotropic drugs. *Am J Cardiol* 1967; **37:** 223–30.
17 Singh BN, Gaarder TD, Kanegae T, Goldstein M, Montgomerie JZ, Mills H. Liquid protein diets and *Torsade de Pointes*. *JAMA* 1978; **240:** 115–9.
18 Jervell A, Lange-Nielsen F. Congenital deaf-mutism

functional heart disease with prolongation of the Q-T interval and sudden death. *Am Heart J* 1957; **54:** 59–68.

19 Levine SA, Woodworth CR. Congenital deaf-mutism, prolonged QT interval, syncopal attacks and sudden death. *N Engl J Med* 1958; **259:** 412–7.

20 Romano C, Gemme G, Pongigilione R. Aritimie cardiache rare dell'eta' pediatrica. II. Accessi sincopali per fibrillazione ventricolare parossistica (presentazione del primo caso della letteratura pediatrica Italiana). *Clin Pediatr Bologna* 1963; **45:** 656–83.

21 Ward OC. A new familial cardiac syndrome in children. *J Ir Med Assoc* 1964; **54:** 103–6.

22 Han J, Millet D, Chizzonitti B, Moe GK. Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate. *Am Heart J* 1966; **71:** 481–7.

23 Chiche P, Haiat R, Steff P. Angina pectoris with syncope due to paroxysmal atrioventricular block: role of ischaemia. Report of two cases. *Br Heart J* 1974; **36:** 577–81.

24 Finley JP, Radford DJ, Freedom RM. *Torsade de pointes* ventricular tachycardia in a newborn infant. *Br Heart J* 1978; **40:** 421–4.

25 Evans TR, Curry PVL, Fitchett DH, Krikler DM. "Torsade de Pointes" initiated by electrical ventricular stimulation. *J Electrocardiol* 1976; **9:** 255–8.

26 Gupta PK, Lichstein E, Chadda KD. Lidocaine-induced heart block in patients with bundle-branch block. *Am J Cardiol* 1974; **33:** 487–92.

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Effect of nifedipine on exercise tolerance in angina pectoris

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SUMMARY Nifedipine is a new antianginal drug, the calcium-antagonistic inhibitory action on excitation-contraction coupling apparently being so pronounced that, in therapeutic dosage, all other pharmacological properties are negligible. Its effect on exercise tolerance in angina was assessed by an exercise study involving 14 patients: single-stage exercise tests were chosen and the advantages of this are given. Our results suggest that the onset of action occurs after about 20 minutes, reaches a peak of activity at approximately one-half to two hours, and some effect may still be present at three hours. There was a significant improvement in exercise times with a mean rise of 50 per cent over placebo.

In recent years various antianginal drugs have been introduced which inhibit the flow of calcium ions across the membrane of the myocardial cell. Earlier examples were verapamil and prenylamine. Nifedipine is the latest and most potent of this class.[1] It restricts calcium ion influx across the cell membrane during excitation so that contraction of both cardiac and vascular smooth muscle is affected.[1 2] Laboratory studies have confirmed that it reduces the tone of vascular smooth muscle, including that of the coronary arteries, and has a negative inotropic effect on the isolated myocardium.[3] In man a drop in peripheral vascular resistance occurs but in therapeutic dose no negative inotropic effect results. In normal resting subjects coronary blood flow, as measured by Xenon 133 uptake, shows an overall increase of 30 to 40 per cent and in patients with coronary arterial disease from 0 to 30 per cent.[4] In resting subjects with normal coronary arteries this is associated with a rise in coronary sinus oxygen saturation,[5] showing that the increase in flow is not simply a physiological response to increased myocardial oxygen demand. Ekelund and Atterhog[6] exercised 10 patients with angina pectoris on a bicycle ergometer and showed significant improvement in exercise tolerance with nifedipine as compared with placebo. Our report is an exercise study using a treadmill and its aims were to establish whether or not nifedipine was an active antianginal agent and to ascertain the duration and intensity of action of the drug.

Subjects and methods

Eighteen patients were investigated, of whom 14 completed the trial. Details of the investigation to which the patient was to be submitted were explained to each patient and his or her signed informed consent was obtained. Ten were men and four were women. The age range was 43 to 71 years (mean 57). The duration of anginal symptoms was five months to eight years (mean three years two months). All had electrocardiograms consistent with the presence of myocardial ischaemia, either at rest or on exercise. All were in a stable phase with no myocardial infarction within the previous 12 months. Early in our screening of volunteers, we found a poor correlation between daily frequency of attacks and ease of provoking angina in the laboratory. The suitability of patients was therefore decided on exercise performance rather than upon symptoms. During the test week the only other medication permitted was sublingual glyceryl trinitrate which was omitted before the daily tests. No patient had electrocardiographic evidence of left bundle-branch block or left ventricular hypertrophy, and none was receiving digitalis. Patients were also excluded with valvar heart disease and with a history of heart failure. The exercise apparatus was a motor-driven treadmill, adjustable for speed and slope (PK Morgan Limited, Chatham). It had an emergency stop button for the patient and a safety harness triggering an automatic cut-out. Factors which might influence exercise tolerance were controlled: the patients were asked not to smoke on those days on which they would be exercised; the first exercise of each day was at

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approximately the same time, namely one and one-half to two hours after the previous meal which was similar in content on each day; the treadmill and laboratory furniture were kept in the same position; the investigators were the same each day; the laboratory was kept at the same temperature and no person unknown to the patient was allowed to enter the room during the tests.

Each patient was investigated for five consecutive days and on each day was exercised from rest to the onset of angina. Exercise was terminated as soon as angina had begun. The time from rest to the onset of angina was recorded. The radiotelemetric electrocardiograph was carefully monitored throughout the procedure, the recording electrode being in the V5 position and the indifferent electrode was below the manubrium sterni. Exercising was repeated from three to six times each day with intervening rest periods of never less than 20 minutes.

The first three days were spent in familiarising the patient with the treadmill and determining the most suitable speed and slope which would repeatedly induce angina between 80 and 120 seconds from rest. On day one each patient began with a multistage test in which walking was started at 2 km/h and increased stepwise by 2 km/h at three minute intervals until angina pectoris was induced. Subsequent tests were single-stage procedures in which the patient was exercised at the speed of that three minute period during which angina pectoris was induced. Further adjustments in speed and slope were then made until the symptom was regularly induced within the desired 80 and 120 seconds. On days four and five each exercise was carried out at this predetermined load.

Treatment on day four was single-blind. After the first exercise each patient was given a placebo capsule which was identical in appearance and peppermint taste to nifedipine but was told that it could be either. He was asked to bite the capsule and keep the fluid in the mouth as long as possible to aid buccal absorption. Exercising was then repeated as on previous days, up to another six times at the same speed and slope. The times taken from resting to the onset of angina were recorded.

Treatment on day five was double-blind. Procedures on day five were exactly similar to day four except that some patients (group A) had 10 mg nifedipine and others (group B) had a placebo. Patients were allocated in a random fashion into one or other group. The data were assessed by analysis of variance.

Results

Of the 14 patients who completed the study, 13 showed an obvious tendency to an increased exercise

Table 1 *Details of exercise tests of 14 patients with angina pectoris*

Case no.	*Slope (°)*	*Speed (kph)*	*Capsule given (h)*	*Exercise*	*Day 4*						
					1	*2*	*3*	*4*	*5*	*6*	*7*
1*	12	4	D4 14.28	Starting time (h)	14·20	14.47	15.09	15.30	15.59	16.25	—
			D5 14.28	Duration (s)	80	98	83	87	79	75	—
2*	6	3	D4 14.25	Starting time (h)	14.16	14.40	15.05	15.31	16.00	16.22	16.
			D5 14.28	Duration (s)	80	90	92	56	40	70	95
3	10	5	D4 10.25	Starting time (h)	10.14	10.55	11.28	12.00	12.30	—	—
			D5 10.28	Duration (s)	100	85	95	90	100	—	—
4*	7	5	D4 10.50	Starting time (h)	10.47	11.15	11.45	12.27	13.00	—	—
			D5 10.43	Duration (s)	85	85	95	115	135	—	—
5	7	5	D4 11.03	Starting time (h)	11.01	11.20	11.58	12.45	—	—	—
			D5 11.06	Duration (s)	70	100	100	90	—	—	—
6*	10	5	D4 10.23	Starting time (h)	10.13	10.44	11.10	11.37	12.09	—	—
			D5 10.09	Duration (s)	105	110	113	111	100	—	—
7	12	5	D4 10.28	Starting time (h)	10.15	10.48	11.26	11.48	12.24	—	—
			D5 10.18	Duration (s)	90	105	90	95	85	—	—
8	8	2	D4 10.52	Starting time (h)	10.40	11.15	11.43	12.16	12.46	—	—
			D5 10.47	Duration (s)	62	66	63	73	65	—	—
9*	12	6	D4 10.40	Starting time (h)	10.25	11.02	11.45	12.07	12.40	—	—
			D5 10.45	Duration (s)	77	75	80	87	80	—	—
10	8/9	2	D4 10.47	Starting time (h)	10.36	11.15	11.43	12.10	12.35	—	—
			D5 10.37	Duration (s)	85	75	82	84	95	—	—
11	8	4	D4 10.30	Starting time (h)	10.27	11.05	11.35	12.05	12.26	—	—
			D5 10.49	Duration (s)	67	62	60	75	67	—	—
12*	10	6	D4 14.29	Starting time (h)	14.21	15.05	15.28	15.53	—	—	—
			D5 14.52	Duration (s)	118	120	125	126	—	—	—
13*	12	5	D4 10.37	Starting time (h)	10.18	10.50	11.20	11.50	12.18	—	—
			D5 10.23	Duration (s)	130	148	142	135	145	—	—
14	10	4	D4 15.10	Starting time (h)	14.52	15.32	15.59	16.38	—	—	—
			D5 14.51	Duration (s)	80	80	84	72	—	—	—

D4, day 4; D5, day 5. * Nifedipine on day 5. Endpoint: onset of angina pectoris.

tolerance during the training days, and exercise loads necessarily were increased to keep the time from resting to the onset of angina pectoris within the required limits. This was not possible in two patients without uncomfortable speeds and slopes and longer times were permitted. In six patients the improvement in exercise tolerance with training was such that the workloads had to be increased on day three. Thus a test of less than five days would have been inadequate.

Table 1 gives the details of the exercise tests in 14 patients with angina pectoris. The time in hours refers to the 24 hour clock and the duration of each exercise test is recorded in seconds. It will be noted that every effort was made to make the exercise tests on day 5 comparable with those on day 4.

Seven patients received the placebo on day four and nifedipine on day five (group A). The other seven had placebo both days (group B). Table 2 shows the longest times walked by each patient after each capsule (max time) compared with the precapsule times (base time). In group A patients, on day four (placebo), the improvements ranged from 7 to 59 per cent, with a mean of 20 per cent (Table 2). On day five (nifedipine) the improvements ranged from 17 to 186 per cent, with a mean of 70 per cent. The extremes of the ranges are from the same two patients. The difference between the improvements is statistically significant; SE $\pm 21{\cdot}79$, $t = 2{\cdot}27$, $p < 0{\cdot}05$ (5% value of t with 12° freedom is $2{\cdot}18$). The changes in performance in group B patients (placebo on both days) ranged from a 0 to 43 per cent improvement on day four (mean 15%) and from a 6 per cent decrease to an increase of 75 per cent on day five (mean 19%): the difference between these improvements is insignificant; $t = 0{\cdot}35$. In group A patients (nifedipine) the mean improvement of day five over day four was 50 per cent (range 10 to 127%) and in group B (placebo) 4 per cent (range −18 to +32%). This difference is significant: SE $\pm 16{\cdot}4$, $t = 2{\cdot}77$, $p < 0{\cdot}05$.

Day 5						
1	*2*	*3*	*4*	*5*	*6*	*7*
14.18	14.46	15.07	15.29	15.56	16.18	—
77	110	115	100	110	95	—
14.18	14.40	15.05	15.25	15.58	16.20	16.42
70	100	120	122	103	115	45
10.15	10.53	11.26	11.50	12.20	—	—
102	128	130	110	105	—	—
10.35	11.16	11.51	12.25	13.00	13.32	—
105	140	195	225	300	240	—
10.53	11.33	12.06	12.41	13.14	—	—
100	175	150	95	100	—	—
9.58	10.35	11.06	11.38	12.01	12.37	13.00
112	185	190	190	170	165	175
10.05	10.47	11.15	11.38	12.02	12.28	—
100	85	105	107	100	90	—
10.37	11.08	11.41	12.09	12.37	—	—
52	52	58	56	65	—	—
10.28	11.05	11.38	12.07	12.48	—	—
76	90	97	105	94	—	—
10.27	10.57	11.22	11.45	12.10	—	—
105	80	100	102	95	—	—
10.46	11.10	11.35	11.58	12.25	—	—
68	63	58	64	58	—	—
14.42	15.19	15.46	16.13	—	—	—
133	155	155	135	—	—	—
10.02	10.33	11.08	11.38	12.07	—	—
133	148	205	166	170	—	—
14.38	15.06	15.35	16.11	—	—	—
88	88	70	95	—	—	—

In group A patients, except for one (case 13) the difference between nifedipine and placebo response was apparent with the first exercise after treatment (Table 3). Mean improvements were 7·5 per cent with placebo and 32·9 per cent with nifedipine. Intervals between treatment and the first exercise thereafter were very variable over the group (10 to 36 minutes) but relatively constant for each patient. The corresponding improvements for group B were 5·8 per cent (day four) and 7·7 per cent (day five).

In group A the time interval between giving nifedipine and the longest exercise time before the onset of pain (maximum time) varied from 29 to 140 minutes with a mean of 74 minutes (Table 4). The best times after placebo in the same patients were obtained between 15 and 141 minutes with an almost identical mean of 75·7 minutes. Thus, though there was an improved performance with nifedipine, the timing of the peak, on average, did not differ from that obtained with placebo.

It had been our intention that on day five exercises should be continued until performance figures had fallen from the peak or maximum values to near base values; thereby we would have had an estimate of duration of action. Unfortunately, none of our patients taking nifedipine was able to exercise for more than twice after their peak values because of fatigue and only one of them, our poorest responder (case 12), had performance figures approaching base times. The last exercises were performed between 83 and 184 minutes after treatment (Table 4).

In this acute study there were no significant side effects. One group A patient felt flushed and had mild headache both days but was worse on placebo. Another had headache on placebo but not on nifedipine. A third patient had dryness of the mouth on nifedipine.

Discussion

Tests involving reproducible exercise are frequently

Table 2 *Exercise times of 14 patients with angina pectoris*

Group A

Case no.	*Day 4 (placebo)* Base time (s)	Max time (s)	Improvement (%)	*Day 5 (nifedipine 10 mg)* Base time (s)	Max time (s)	Improvement (%)
1	80	98	23	77	115	49
2	80	95	19	70	122	74
4	85	135	59	105	300	186
6	105	113	8	112	190	70
9	77	87	13	76	105	38
12	118	126	7	133	155	17
13	130	148	14	133	205	54
Mean			20			70

Group B

Case no.	*Day 4 (placebo)* Base time (s)	Max time (s)	Improvement (%)	*Day 5 (placebo)* Base time (s)	Max time (s)	Improvement (%)
3	100	100	0	102	130	27
5	70	100	43	100	175	75
7	90	105	17	100	107	7
8	62	73	18	52	65	25
10	85	95	12	105	102	−3
11	67	75	12	68	64	−6
14	80	84	5	88	95	7
Mean			15			19

used in order to assess the efficacy of antianginal drugs. Birkett and Chamberlain[7] believe exercise studies to be of greater value than carefully designed prolonged double-blind trials. In long-lasting trials consumption of glyceryl trinitrate may inadequately reflect changes in effort tolerance, particularly in patients who limit its use because of side effects.[8] The frequency of attacks may not decrease with increased effort tolerance if this leads to greater activity, as shown in this study. A drug which increases effort tolerance should be of value to patients with angina pectoris even when, because of increased activity, neither the number of attacks nor the amount of glyceryl trinitrate consumed are reduced. An exercise study of the present design also involves each patient for a shorter time than a prolonged trial, so that he is off possibly more efficacious treatment for a shorter period and is, therefore, at less risk.

Single stage tests[7 9] may be more meaningful than multistage tests[10] in quantifying changes in exercise performance, as they take account of haemodynamic responses induced by exercise. It has been shown that the triple product of heart rate × ejection × systolic aortic root pressure is proportional to myocardial oxygen consumption[11 12] and achieves a constant level for each patient at the onset of angina unless excessive workloads are used.[13] When a patient is exercised at a constant workload from rest, the rate of increase in triple product is maximal at the onset lessening as exercise continues and reaches a plateau with steady state in about four minutes.[13] The graphical recording of this response approximates to an inverted exponential curve (Fig. 1 and 2). Thus, if the level of triple product at which angina occurs is achieved early at a particular workload, any improvement caused by treatment may, on re-exercising at the same workload, lead to only a short delay in the onset of symptoms (Fig. 1, A^1 and A^2; and Fig. 2, A). Conversely, if the anginal threshold is reached at a time approaching the steady state the same therapeutic intervention would cause a much longer delay in the onset of pain and indeed, at that particular workload, might prevent its occurrence entirely (Fig. 1, B^1 and B^2; and Fig. 2, B). It is thus misleading to regard the difference between the time of onset of angina pectoris before and after a therapeutic intervention as a linear measure of improvement. Indeed it will be seen that any such difference is of greater

Table 3 *Percentage improvement of first exercise time after taking capsule compared with pre-capsule exercise time (base time) and interval between taking capsule to exercise*

Group A

Case no.	*Day 4 placebo* %	Min	*Day 5 nifedipine 10 mg* %	Min
1	22·5	19	42·9	18
2	12·5	15	42·9	12
4	0	25	33·0	33
6	4·76	21	65·2	26
9	−2·6	22	18·4	20
12	1·7	36	16·5	27
13	13·8	13	11·3	10
Mean	7·5		32·9	

Group B

Case no.	*Day 4 placebo* %	Min	*Day 5 placebo* %	Min
3	−15	30	25·5	25
5	42·8	17	75·0	22
7	16·6	20	−15·0	29
8	6·45	23	0	21
10	−2·6	22	−24·0	20
11	−7·5	35	−7·35	21
14	0	22	0	15
	5·8		7·7	

Table 4 *Time interval between taking capsule and longest exercise time to demonstrate improvement; group A took placebo and nifedipine and group B took only placebo*

Group A				*Group B*		
Case no.	*Times of max time after taking capsule*		*Duration of improvement day 5 (min)*	*Case no.*	*Times of max time after taking capsule*	
	Day 4 placebo (min)	*Day 5 nifedipine 10 mg (min)*			*Day 4 placebo (min)*	*Day 5 placebo (min)*
1	20	40	111	3	126	60
2	141	59	114	5	20	30
4	135	140	120	7	21	81
6	48	60	184	8	85	51
9	85	83	124	10	109	69
12	86	29	83	11	96	70
13	15	107	107	14	50	81
Mean	75·7	74			72·4	63·1

significance if the time of onset of angina before the therapeutic intervention is of short duration. For example, an improvement of 20 seconds occurring when the time to angina is 80 seconds from the onset of exercise is of greater significance for suggesting improvement than a similar 20 second delay occurring when the time from resting to angina pectoris before the therapeutic intervention is 180 seconds.

From examination of the curves in Fig. 1 and 2, it will be seen that the ratio of the time to angina pectoris after therapeutic intervention to that before that intervention is almost constant for a particular patient at different workloads. The difference, maximum time minus base time, lessens with higher loads, but the ratio of the two remains fairly constant. This method makes feasible the comparison of improvements of different patients with different times to angina pectoris before a therapeutic intervention. It can only apply if the workload is constant and the same for both test drugs and placebo.

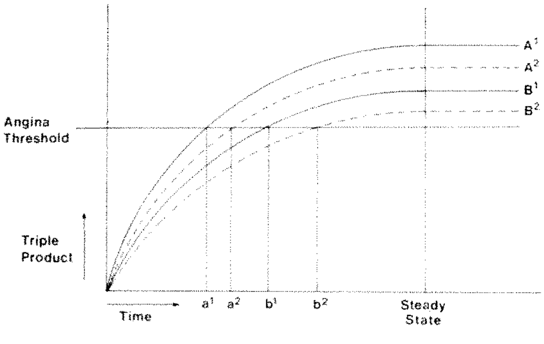

Fig. 1 *This applies to an antianginal drug which lowers peripheral vascular resistance and therefore triple product (TP) response to exercise, without altering TP at anginal onset.* A^1 *and* B^1 *are TP response of same patient before treatment to different work loads.* A^2 *and* B^2 *are the corresponding responses after the same treatment.* $(a^2/a^1 = b^2/b^1)$ *but* $a^2 - a^1$ *is less than* $b^2 - b^1$.

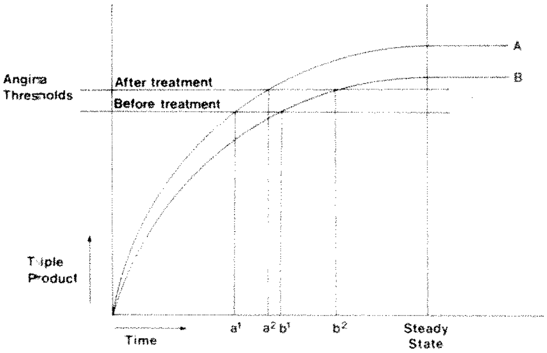

Fig 2 *This applies to a drug which increases coronary arterial flow and therefore TP at anginal onset, leaving peripheral vascular resistance unaltered.* $(a^2/a^1 = b^2/b^1)$ *more closely than* $a^2 - a^1 = b^2 - b^1$.

The drawback of the method is that it requires that the times to the onset of angina under constant conditions should be reproducible within fairly fine limits. Otherwise, natural fluctuation plus therapeutic effect may lead to steady state being reached before anginal onset. Moreover, the natural fluctuation and improvement previously mentioned are such that the patient has to be exercised several times before a work level is achieved which will precipitate angina pectoris every time between 80 and 120 seconds. In most of our patients this was achieved on exercise testing after two days, but in six of them a third day was required to achieve this reproducibility. In most patients the variation was over 50 per cent on the first day and it was not until day three that the results were reproducible with a 10 to 15 per cent range.

The placebo response of between 15 and 20 per cent in our patients is high for an acute study[13–15] but may reflect the sensitivity of the method. Natural fluctuation in exercise tolerance and the tendency of it to improve after the first exercise could account for this. The close reproducibility of placebo response, however, increases the significance of the 50 per cent difference between nifedipine and placebo. This compares very favourably with similar studies carried out on beta-blockers.[7 9]

Subjective improvement, as shown by increased effort tolerance, was accompanied by a corresponding delay in the appearance of ischaemic ST segment depression or T wave changes in the effort electrocardiogram, indicating that nifedipine acts by causing a reduction in myocardial hypoxia for a given degree of exercise, rather than by suppressing anginal pain.

We were unable to give an accurate indication of the duration of action of nifedipine in the treatment of angina pectoris. As mentioned, we had planned that on day five exercises should be continued until the performance figures had fallen from the maximum values to near baseline values. None of our patients receiving nifedipine was able to exercise for more than two periods after their peak values because of fatigue, and only one of them, our poorest responder (case 12), had performance figures approaching base times. The last exercises were performed between 83 and 184 minutes after treatment (Table 4). Our results suggest, however, that the onset of action of nifedipine occurs after about 20 minutes, reaches a peak of activity at approximately one-half to two hours, and some effect may still be noted at three hours. This compares with a time of onset between five and 10 minutes for sublingual glyceryl trinitrate or isosorbide dinitrate, with a duration of action of approximately 90 minutes and 120 minutes, respectively.[16]

It is of interest that though there was an improved performance with nifedipine, the timing of the peak, on average, did not differ from that obtained with placebo. Table 1 shows the development of this peak for both nifedipine and placebo-treated patients. It suggests that the observation is at least in part the result of the warm-up phenomenon. It will be noted, however, that the peak, as well as being higher, is maintained in those patients receiving nifedipine whereas it falls away in those receiving placebo. Maintenance of the improvement, therefore, appears to be associated with the active therapeutic intervention.

Our findings suggest that nifedipine is an active antianginal agent and that its action is more prolonged than glyceryl trinitrate or isosorbide dinitrate. The evidence justifies its further clinical evaluation as an antianginal agent.

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References

1 Fleckenstein A, Tritthart H, Döring HJ, *et al.* BAY a 1040—ein hochaktiver Ca-antagonistischer Inhibitor der elektro-mechanischen Koppelungsprozesse im Warmblüter-Myokard. *Arzneim Forsch* 1972; **22:** 22–33.

2 Grün G, Fleckenstein A. Die elektromechanische Entkoppelung der glatten Gefässmuskulatur als Grundprinzip der Coronardilatation durch 4-(2′-Nitrophenyl)-2,6-dimethyl-1, 4-dihydropyridin-3, 5-dicarbonsäure-dimethylester (BAY a 1040 Nifedipine). *Arzneim Forsch* 1972; **22:** 334–44.

3 Vater W, Kroneberg G, Hoffmeister F, *et al.* Zur Pharmakologie von 4-(2′-Nitrophenyl)-2, 6-dimethyl-1, 4-dihydropyridin-3, 5-dicarbonsäuredimethylester (Nifedipine), BAY a 1040. *Arzneim Forsch* 1971; **22:** 1–14.

4 Heeger H, Kahn P, Aldor E. Myocardial circulation under Adalat in different phases of coronary diseases. In: Lochner W, Braaschw, Kroneberg G, eds. *New therapy of ischaemic heart disease.* Berlin, Heidelberg, New York: Springer-Verlag, 1975: 204–10.

5 Kohler JA. The effect of Adalat on coronary circulation after sublingual administration. In: Lochner W, Braasch W, Kroneberg G, eds. *New therapy of ischaemic heart disease.* Berlin, Heidelberg, New York: Springer-Verlag, 1975: 234–5.

6 Ekelund LG, Atterhog JH. Adalat and beta blockers; the mechanism studied with two series of work tests in two groups of patients with angina pectoris. In: Lochner W, Braasch W, Kroneberg G, eds. *New therapy of ischaemic heart disease.* Berlin, Heidelberg, New York: Springer-Verlag, 1975: 169.

7 Birkett DA, Chamberlain DA. Beta-adrenergic blockade in angina pectoris: a method of treadmill assessment. *Br Med J* 1966; **ii:** 500–2.

8 National Research Council. Division of Medical Sciences Drug Efficacy Study. Final Report to the Commissioner of Food and Drugs, Food and Drug Administration. Washington DC: National Academy of Sciences, 1969: 161.

9 Coltart DJ. Comparison of effects of propranolol and practolol on exercise tolerance in angina pectoris. *Br Heart J* 1971; **33:** 62–4.

10 Dagenais GR, Mason RE, Friesinger GC, Wender C, Ross RS. Exercise tolerance in patients with angina pectoris: daily variation and effect of pentaerythritol tetranitrate. *John Hopkins Med J* 1969; **125:** 301–11.

11 Robinson BF. Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation* 1967; **35:** 1073–83.

12 Robinson BF. Mode of action of nitroglycerin in angina pectoris. Correlation between haemodynamic

effects during exercise and prevention of pain. *Br Heart J* 1968; **30:** 295–302.

13 Redwood DR, Rosing DR, Goldstein RE, Beiser GD, Epstein SE. Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris. *Circulation* 1971; **43:** 618–28.

14 Wilson AG, Brooke OG, Lloyd HJ, Robinson BF. Mechanism of action of beta-adrenergic receptor blocking agents in angina pectoris: comparison of action of propranolol with dexpropranolol and practolol. *Br Med J* 1969; **i:** 399–401.

15 Christensson B, Karlefors T, Westling H. Haemodynamic effects of nitroglycerin in patients with coronary heart disease. *Br Heart J* 1965; **27:** 511–9.

16 Goldstein RE, Rosing DR, Redwood DR, Beiser GD, Epstein SE. Clinical and circulatory effects of isosorbide dinitrate. Comparison with nitroglycerin. *Circulation* 1971; **43:** 629–40.

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Br Heart J 1980; **44**: 342–8

Prospective study of heart disease in untreated maturity onset diabetics

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SUMMARY Frequent abnormalities of left ventricular function were demonstrated by systolic time intervals and M-mode echocardiography in 69 maturity onset diabetics without clinical heart disease before and during standard hypoglycaemic treatment.

The response of the ratio of pre-ejection period (PEP) to left ventricular ejection time (LVET) during the first two months of treatment identified two groups of patients. Group A had a normal or slightly raised ratio which fell with treatment. In group B the ratio was significantly higher and did not change even after four months treatment. The change in group A was thought to be a result of the improvement in blood glucose, as the correlation between the random blood glucose before treatment and PEP/LVET ratio was lost with reduction of hyperglycaemia. The persistently raised PEP/LVET in group B suggested significant left ventricular dysfunction.

Abnormalities of the diastolic closure rate and isovolumic relaxation time were frequently detected and in only nine of 69 patients were both within 2 SD from normal. They were more pronounced in group B and were significantly different from group A and normal subjects.

Group B could be subdivided into six patients (group B_1) with outward wall motion in isovolumic relaxation and delayed aortic valve closure caused by incoordination and nine (group B_2) who did not show these changes. An exercise electrocardiogram was positive in two of five group B_1 patients and negative in the seven tested in group B_2. Three patients in group B_2 and one in group A had clinically apparent diabetic microvascular disease.

Coronary artery disease was common and seven patients (six in group B_1 and one in group A) demonstrated left ventricular wall dyskinesis in the absence of symptoms; 11 of the original group of 110 were excluded because of symptomatic disease. A smaller group had slow ejection and relaxation, probably a result of increased left ventricular stiffness from myocardial involvement by diabetic microvascular disease.

Cardiovascular disease is a major cause of morbidity and mortality in patients with maturity onset diabetes.[1 2] Coronary artery disease is common[1] but diabetics can develop abnormalities of myocardial function with patent main coronary arteries,[3 4] which may progress to cardiomyopathy and chronic heart failure. This may be part of the generalised microvascular disease which causes retinopathy, neuropathy, and nephropathy.[5–9] Histological studies of myocardium have shown that abnormalities of small vessels[5 6 10] and capillary basement membrane[11] are common. No information is available on whether the duration of diabetes is important in the development of left ventricular dysfunction and chronic heart failure or if the progression of heart disease can be influenced by hypoglycaemic therapy.

Systolic left ventricular function can be measured by systolic time intervals and M-mode echocardiographic indices of ejection. Abnormalities of these have been shown in both diabetics without clinical heart disease[7 8] (especially those with proliferative retinopathy and nephropathy) and patients with coronary artery disease,[12] in whom it indicates a poor prognosis.[13] Changes in systolic time intervals have been noted with treatment of recently diagnosed diabetics.[14] Diastolic left ventricular function

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can be evaluated by measuring the time relations of various events in the cardiac cycle (aortic valve closure, mitral valve opening, and minimal dimension) and the associated left ventricular wall motion.[15] [16] Disturbed ventricular filling in young asymptomatic diabetics[9] and patients with hypertension[16] can be differentiated from the segmental abnormalities which are the cause of impaired left ventricular function in coronary artery disease.

This study was designed to investigate by simple non-invasive methods untreated maturity onset diabetics to determine the prevalence of left ventricular dysfunction and whether it is influenced by standard hypoglycaemic therapy and can be differentiated from coronary artery disease.

Patients

Consecutive patients between 30 and 65 years who presented to the Dudley Road Hospital Diabetic Clinic with clinical symptoms of diabetes and a random blood glucose greater than 11·1 mmol/l, a fasting glucose greater than 6·1 mmol/l, or a blood glucose greater than 11·1 mmol/l two hours after a 50 g oral glucose tolerance test and who had received no hypoglycaemic therapy previously were considered for inclusion in the study.

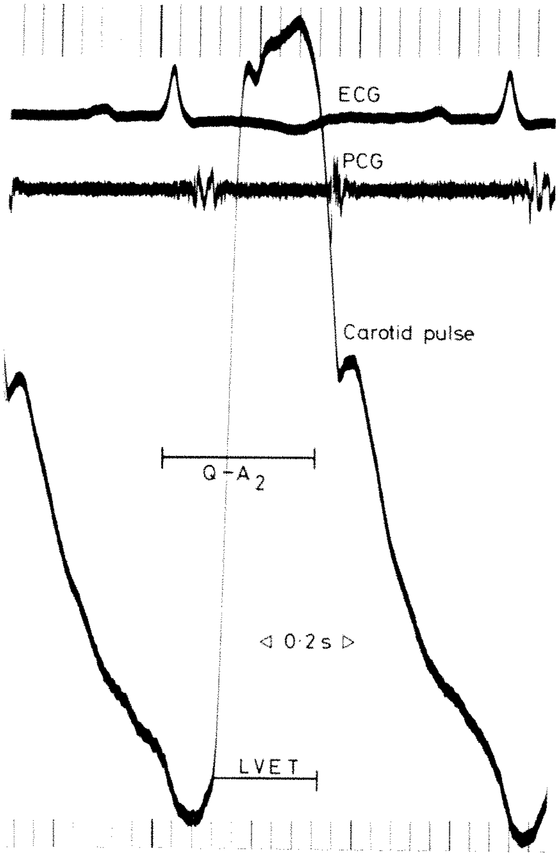

Fig. 1 *Simultaneous electrocardiogram (ECG), phonocardiogram (PCG), and indirect right carotid pulse. Q-A_2, electromechanical systole; LVET, left ventricular ejection time.*

Initial assessment included clinical examination, electrocardiogram, chest radiography, and routine biochemistry (urea and electrolytes, liver function tests, and cholesterol), and patients with the following conditions were excluded:

(1) Coronary artery disease, that is angina of effort or previous myocardial infarction. Resting electrocardiographic abnormalities suggestive of ischaemic heart disease including infarction, bundle-branch block, and ST segment abnormalities.
(2) Presence of a disease known to influence left ventricular function (thyroid disease, alcoholism, hypertrophic obstructive cardiomyopathy, and hypertension (BP > 145/95 mmHg).
(3) Chronic heart failure, clinical heart disease (peripheral oedema, gallop rhythm, auscultatory abnormalities), and a cardiothoracic ratio > 55 per cent or other chest *x*-ray abnormalities
(4) Peripheral vascular disease.
(5) Heavy cigarette smokers > 20/day.
(6) Hypercholesterolaemia (serum cholesterol > 7·0 mmol/l).

Methods

Systolic time intervals were obtained (after Weissler *et al.*[17]) in the early afternoon on a Cambridge multichannel photographic recorder at paper speed 100 mm/s. The $Q - A_2$ (time interval from Q wave of the electrocardiogram to the onset of the aortic second heart sound) and left ventricular ejection time (LVET) were measured in ms (Fig. 1) and the following were derived:

Pre-ejection period (PEP) = $(Q - A_2) -$ LVET
and ratio of PEP/LVET

The latter ratio was used and not the heart rate corrected indices because of the wide range of resting heart rates in the diabetic subjects.

Echophonocardiography was performed with simultaneous electrocardiogram (standard lead II) in the partial left laterial position using an Ekoline SK20 Ultrasonoscope at paper speed 100 mm/s. The early diastolic closure rate was determined in mm/s from the slope E – Fo of the mitral valve at its point of maximal excursion. The isovolumic relaxation time was determined in ms from the onset of the aortic sound to the point of rapid anterior motion of the anterior mitral valve cusp. Left ventricular dimensions in diastole (DD) (at R wave of electrocardiogram), minimal dimension (DS), and at the point of mitral valve opening were determined. The time interval between the aortic second sound and minimal dimension was measured (Fig. 2). The following were derived:

$$\%\ \text{fractional shortening} = \frac{\text{DD} - \text{DS}}{\text{DD}} \times 100$$

$$\%\ \text{dimension change during isovolumic period} =$$

$$\frac{\text{dimension at mitral valve opening} - \text{DS}}{\text{DD} - \text{DS}} \times 100$$

When required, a continuous multistage exercise electrocardiogram was performed using a graded bicycle ergometer with an initial workload of 300 kpm/min rising by increments of 300 kpm at three minute intervals. The electrocardiogram was continuously monitored and sampled at three minute intervals until 85 per cent predicted maximal heart rate was achieved, and during nine minutes rest.

All patients while on treatment had a reassessment of clinical features, blood glucose, echocardiogram, and systolic time intervals at approximately two months, and a selected group at four months.

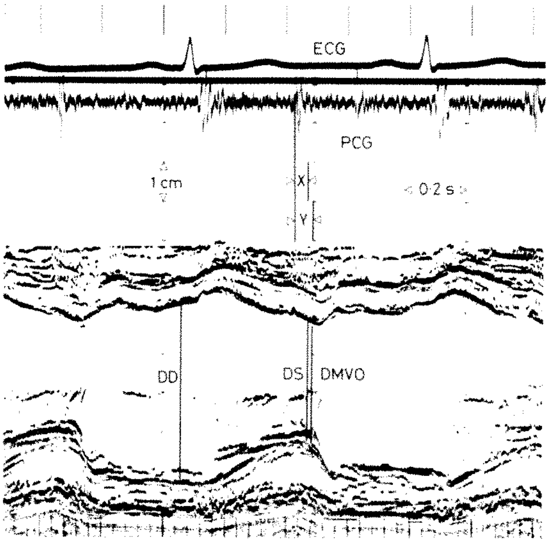

Fig. 2 *Left ventricular echocardiogram of normal subject with simultaneous electrocardiogram (ECG) and phonocardiogram (PCG). DD, diastolic dimension; DS, systolic dimension; DMVO, dimension at mitral valve opening; Y, isovolumic relaxation time; X, interval from aortic second sound to minimal dimension.*

Table 1 *Age and sex of groups (mean ± SD)*

	All untreated diabetics *n* = 69	*Group A* *n* = 54	*Group B* *n* = 15	*Normal* *n* = 50	*Angina* *n* = 25
Age (y)	54 ± 5	55 ± 3	53 ± 2	56 ± 3	58 ± 4
Sex F	37	29	8	30	14
M	32	25	7	20	11

Echocardiography and the determination of systolic time intervals were also performed in two age- and sex-matched control groups (Table 1): (1) 50 normal subjects; (2) 25 patients with typical angina of effort without clinical or electrocardiographic evidence of myocardial infarction or cardiomegaly on radiography.

The echocardiograms and systolic time intervals were numerically coded by an independent observer and interpreted blind by LMS.

Pearson's correlation coefficient and paired and Student's t tests were used to analyse the differences between the incremental and prevalence scores.

Results

One-hundred-and-ten patients presented during the course of the study of whom 41 were excluded (11 with coronary artery disease, nine with hypertension, three with peripheral vascular disease, four with previous thyroid disease, three heavy smokers, one with acromegaly, one with chronic heart failure, eight poor echocardiogram quality, and one with a calcified bicuspid aortic valve). Among those included in the study, two patients had background retinopathy, one had significant proteinuria, and one had a sensory peripheral neuropathy. The values quoted are mean ± one standard deviation.

In the untreated group PEP/LVET (0·36 ± 0·06) was significantly different from the normal subjects (0·31 ± 0·004, p < 0·001). The wide range (0·26–0·50) of values correlated with the random blood glucose (Fig. 3) (r = +0·72 p < 0·001). After two months of treatment the correlation coefficient fell to 0·36 (not significant) with a reduction in blood glucose values.

The distribution of PEP/LVET values before treatment was slightly positively skewed. Though there was only an insignificant change of PEP/LVET ratio in the total group (0·36 ± 0·09 to 0·34 ± 0·07) during initial treatment, a bimodal distribution within the sample became evident and identified two subgroups of patients with no overlap of values, designated groups A and B. Group A ($n=54$) had a PEP/LVET ratio either within the range of the control group or which became normal at the two month review (pretreatment $0{\cdot}34 \pm 0{\cdot}04$ and review $0{\cdot}30 \pm 0{\cdot}02$); the change is significant ($p < 0{\cdot}01$). Group B ($n=15$) had a higher pretreatment PEP/LVET ratio which did not significantly change with treatment (pretreatment $0{\cdot}43 \pm 0{\cdot}04$, review $0{\cdot}46 \pm 0{\cdot}02$). Both values were significantly different from the control group and group A ($p < 0{\cdot}001$). After four months' treatment the PEP/LVET ratios were unchanged ($0{\cdot}45 \pm 0{\cdot}03$) (Fig. 4). The diastolic closure rate was reduced in 42 of 69 of the diabetic patients (more than 2 SD from normal) and the isovolumic relaxation time was prolonged in 58 of 69; both were significantly different from normal ($p < 0{\cdot}001$) and there was no change with treatment. The diastolic closure rate and isovolumic relaxation time were significantly different in groups A and B ($p < 0{\cdot}001$) (Table 2). It was possible to subdivide group B into those with a significant dimension change during isovolumic relaxation and associated delayed aortic valve closure, group B$_1$ ($n=6$), and those without, group B$_2$ ($n=9$) (Table 3). One patient in group A demonstrated significant dimension change.

The left ventricular dimensions and fractional shortening were normal in all but five patients. In three (one each in groups A, B$_1$, and B$_2$) the diastolic dimension was greater than 60 mm (2 SD from normal); in the patient in group B$_1$ there was reverse septal motion and reduced fractional shortening. Two other patients showed a reduction in fractional shortening from the normal of 33 ± 5 per cent to 14 per cent (patient in group B$_2$) and 16 per cent (patient in group A).

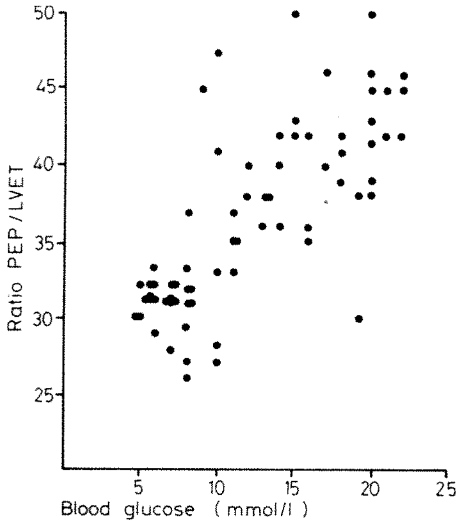

Fig. 3 *Correlation of PEP/LVET ratios and blood glucose in untreated diabetics.* $n=69$, $r=+0{\cdot}72$ ($p < 0{\cdot}001$).

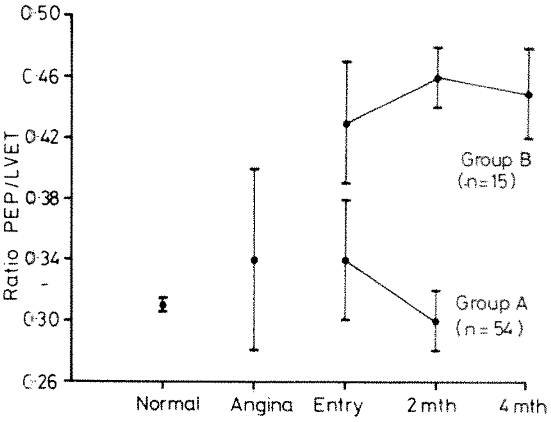

Fig. 4 *Control values and change in PEP/LVET ratio in treated diabetics (mean ± SD).*

Resting electrocardiographic abnormalities were present in ten patients: five had a mean frontal plane QRS axis greater than minus 30 degrees (two patients in B$_1$, three in A), one patient in B$_1$ had poor progression of praecordial R waves, and four had inferior or lateral lead T wave inversion (two in A, one each in B$_1$ and B$_2$).

An exercise electrocardiogram was performed on 12 group B patients four months after presentation; none developed chest pain but two showed 2 mm ST depression in the lateral leads after achieving 85 per cent of the maximal predicted heart rate; both were in subgroup B$_1$.

A significant fall in blood glucose ($p < 0{\cdot}001$) and relief of diabetic symptoms was achieved in both groups by treatment. Initial random blood glucose in group B (14 ± 3 mmol/l) was greater than group A (11 ± 0 mmol/l, $p < 0{\cdot}05$) but there was no difference at review (9 ± 3 and 8 ± 2 mmol/l, respectively). A similar proportion of group A (28 of 54) and group B (eight of 15) were assigned to oral hypoglycaemic agents, there was one patient on insulin in each group and the remainder required diet alone. Group B$_2$ contained all patients with clinically apparent microvascular disease except one with proteinuria who was in group A.

Discussion

Approximately three-quarters of diabetics in Great Britain are of maturity onset type and diabetes affects at least 1 per cent of the population. Heart

Table 2 *Systolic time intervals, diastolic closure rate, and isovolumic relaxation time in control and diabetic groups (mean ±SD)*

	Controls		*Diabetics*					
			Total group n=69		*Group A n=54*		*Group B n=15*	
	Normal n=50	*Angina n=25*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*
PEP/LVET	0·31 ±0·004	0·34 ±0·06	a 0·36 ±0·09	0·34 ±0·07	0·34 ±0·04	b 0·3 ±0·02	a, c, d 0·43 ±0·04	a, c, d 0·46 ±0·92
Diastolic closure rate (mm/s)	90 ±24	a 68 ±20	a 59 ±26	a 62 ±21	a 70 ±12	a 69 ±11	a, c, d 47 ±14	a, c, d 50 ±11
Isovolumic relaxation time (ms)	58 ±9	e 75 ±23	a 84 ±22	a 85 ±24	a 71 ±14	a 69 ±15	a, d 92 ±20	a, f, d 95 ±16

a. Difference from normal, p < 0·001. b. Difference pre- and post-treatment in group A, p < 0·01. c. Difference from angina group, p < 0·001. d. Difference between groups A and B, p < 0·001. e. Difference from normal, p < 0·01. f. Difference from angina group, p < 0·01.

disease is a major cause of morbidity and mortality in this group. We have studied 69 maturity onset diabetics before and during treatment and have shown frequent abnormalities of left ventricular function by non-invasive techniques.

Systolic time intervals are a non-specific indicator of left ventricular systolic function. The response of PEP/LVET identified two groups of patients: in group A PEP/LVET was slightly raised or normal and fell with treatment, in group B it was significantly higher at presentation and did not change. These results confirm the presence of abnormal systolic time intervals previously reported in diabetics before and during initial treatment,[7, 14] but the specific changes were different from the latter study probably because of the dissimilar sample investigated. Though unexpected because of the wide daily fluctuations in blood glucose, the correlation between the PEP/LVET and random blood glucose before treatment indicates a relation between the degree of glucose intolerance and left ventricular dysfunction particularly as it was lost with treatment. We suggest the changes in group A are directly the result of the metabolic effects of hyperglycaemia and are similar to the improvements in abnormal motor conduction velocities[18] and platelet function[19] that have been noted with the initial control of diabetes. The persistently raised PEP/LVET in group B is evidence of significant left ventricular dysfunction which was confirmed by analysis of the diastolic function.

The diastolic closure rate and isovolumic relaxation time have a complex underlying mechanism and show the presence of a non-specific abnormality in early diastole related to filling and relaxation; they are abnormal in many conditions which affect the left ventricle, such as coronary artery disease,[20] hypertrophic obstructive cardiomyopathy,[21] and hypertension.[16, 22] We demonstrated a correlation between these variables ($r = -0{\cdot}73$, $p < 0{\cdot}001$) in the wide range of values. Group B was significantly different from group A and the normals ($p < 0{\cdot}001$) which confirms the presence of abnormal left ventricular diastolic function.

Coronary artery disease usually produced abnormalities of left ventricular function because of the segmental nature of myocardial ischaemia. Contraction loses its co-ordinate mechanism and

Table 3 *Diastolic abnormalities in untreated maturity onset diabetes (mean ±SD)*

	Normal n=50	*Angina n=25*	*Group A n=54*	*Group B n=15*	*Group B_1 n=6*	*Group B_2 n=9*
Relation of aortic valve closure to minimal dimension* (ms)	−40 ±12	a −1 ±23	a, b −16 ±12	a −19 ±33	a +1 ±18	c, d −34 ±13
Outward wall motion in isovolumic period as percentage total dimension change	0	16 ±11	7 ±12	12 ±15	25 ±7	c, d 4 ±2

a. Difference from normal, p < 0·001. b. Difference from angina, p < 0·01. c. Difference from angina, p < 0·001. d. Difference group B_1 from B_2, p < 0·001.

* If negative aortic valve closure precedes minimal left ventricular dimension.

this delays aortic valve closure to the time of minimal left ventricular dimension, prolongs the PEP (index), and increases PEP/LVET.[11 14] A similar incoordinate mechanism in diastole produces a dimension change between minimal left ventricular dimension and the delayed mitral valve opening and, though specific, is an insensitive method of detecting coronary artery disease.[15] Significant outward motion with delayed aortic valve closure was seen in group B_1 and in one patient in group A. Patients in group B_1 also had persistently abnormal PEP/LVET and one had reverse septal motion and reduced fractional shortening. There were resting electrocardiographic abnormalities in four, and in two of the five patients tested there was lateral ST depression on an exercise electrocardiogram. There seems no doubt that this group has asymptomatic coronary artery disease and the abnormalities are a result of left ventricular wall dyskinesis; this fairly gross form of coronary artery disease probably indicates a poor prognosis. The absence of a history of angina or myocardial infarction tends to corroborate the epidemiological[23] and necropsy[24] evidence which suggests that diabetics have a high incidence of unreported myocardial infarctions.

In contrast, group B_2 had similar abnormalities of PEP/LVET, diastolic closure rate, and isovolumic relaxation time but aortic valve closure always preceded minimal left ventricular dimension, and though mitral valve opening was delayed there was no outward wall motion. These abnormalities, which are similar to those described in hypertension[16] and young diabetics,[9] are significantly different from group B_1 and the anginal control group. Thus the patients in group B_2 demonstrated slow ejection and relaxation without the incoordination associated with coronary artery disease. This diffuse left ventricular involvement was present in 13 per cent (nine of 69) of maturity onset diabetics at presentation and was not influenced by hypoglycaemic treatment. It is not possible to exclude the presence of coronary artery disease without coronary arteriography which we could not ethically justify, but seven of the group were exercise tested and none had a positive test. Myocardial histology in diabetics often shows extravascular connective tissue infiltration[10] and small vessel abnormalities[5 6] as a manifestation of microvascular disease. These abnormalities would be expected to increase left ventricular stiffness and produce the slow ejection and relaxation that we have shown. Three of the nine patients had clinically obvious microvascular disease, and it is well known that microvascular disease can be detected by fluorescein angiography[25] and renal biopsy[26] in the absence of clinical evidence of disease. It seems likely that the abnormalities in group B_2 are a result of myocardial involvement by diabetic microvascular disease.

Diastolic abnormalities were more frequent than those in systole, and 60 of 69 patients had either the diastolic closure rate or isovolumic relaxation time outside two standard deviations from the normal. There is a spectrum of abnormality from slight prolongation of isovolumic relaxation time and reduced diastolic closure rate with normal wall motion to the more pronounced abnormalities suggestive of coronary artery disease and asymptomatic cardiomyopathy. Whether the diastolic abnormalities in group A which are at the lower end of the range are the result of either or both of these disease processes is speculative, but there was no clear differentiation between the two groups and in only one patient was there any evidence of incoordinate relaxation. Maturity onset diabetes often has an insidious onset with persistent hyperglycaemia[27] and this is a risk factor for coronary artery disease,[28] but the patients were selected because of normal serum cholesterol and blood pressure and moderate smoking habits, and though there were seven patients with asymptomatic coronary artery disease the probability of significant coronary artery disease in group A is low in the absence of clinical symptoms.[29] Therefore many diabetics may have lesser degrees of myocardial involvement of the type discussed above.

We have shown a range of abnormalities of left ventricular function in diabetics at presentation. Incoordinate left ventricular function was detected in seven and there was symptomatic coronary artery disease in 11 of the original sample. Therefore coronary artery disease occurred frequently, ie 16 per cent or 18 of 110, of whom seven had no chest pain, and as incoordination, clinical history, and resting electrocardiogram are insensitive methods of detecting coronary artery disease, this is an underestimate of its true incidence and emphasises the frequent association of diabetes and coronary artery disease. Group A showed frequent non-specific diastolic abnormalities, the cause of which is unknown. Nine patients had diffuse left ventricular disease with slow ejection and relaxation with no evidence of coronary artery disease, which is suggestive of a myopathic process related to diabetic microvascular disease. Long-term follow-up is in progress to determine the prognosis of group B_1 patients and whether group B_2 patients will develop clinically apparent microvascular disease earlier than other patients or progress to chronic heart failure as predicted from the Framingham study.[2]

References

1 Liebow IM, Hellerstein HK. Cardiac complications of diabetes mellitus. *Am J Med* 1949; **7:** 660–70.

2 Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979; **241:** 2035–8.

3 Regan TJ, Lyons MM, Ahmed SS, *et al.* Evidence for cardiomyopathy in familial diabetes mellitus. *J Clin Invest* 1977; **60:** 885–99.

4 D'Elia JA, Weinrauch LA, Healy WR, Libertins JA, Bradley RF, Leland OS Jr. Myocardial dysfunction without coronary artery disease in diabetic renal failure. *Am J Cardiol* 1979; **43:** 193–9.

5 Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. A new type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 1972; **30:** 595–602.

6 Hamby RI, Zoneraich S, Sherman L. Diabetic cardiomyopathy. *JAMA* 1974; **229:** 1749–54.

7 Ahmed SS, Jaferi GA, Narang RM, Regan TJ. Preclinical abnormality of left ventricular function in diabetes mellitus. *Am Heart J* 1975; **89:** 153–8.

8 Seneviratne BIB. Diabetic cardiomyopathy: the preclinical phase. *Br Med J* 1977; **i:** 1444–6.

9 Sanderson JE, Brown DJ, Rivellese A, Kohner E. Diabetic cardiomyopathy? An echocardiographic study of young diabetics. *Br Med J* 1978; **i:** 404–7.

10 Ledet T. Diabetic cardiomyopathy. Quantitative histological studies of the heart from young juvenile diabetics. *Acta Path Microbiol Scand* [*A*] 1976; **84:** 421–8.

11 Fischer VW, Barner HB, Leskiw ML. Capillary basal laminar thickness in diabetic human myocardium. *Diabetes* 1979; **28:** 713–9.

12 Chen W, Gibson D. Mechanisms of prolongation of pre-ejection period in patients with left ventricular disease. *Br Heart J* 1979; **42:** 304–10.

13 Gillilan RE, Parnes WP, Khan MA, *et al.* The prognostic value of systolic time intervals in angina pectoris patients. *Circulation* 1979; **60:** 268–75.

14 Sykes CA, Wright AD, Malins JM, Pentocost BL. Changes in systolic time intervals during treatment of diabetes mellitus. *Br Heart J* 1977; **39:** 255–9.

15 Upton MT, Gibson DG, Brown DJ. Echocardiographic assessment of abnormal left ventricular relaxation in man. *Br Heart J* 1976; **38:** 1001–9.

16 Chen W, Gibson D. Relationship of isovolumic relaxation to left ventricular wall movement in man. *Br Heart J* 1979; **42:** 51–6.

17 Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation* 1968; **37:** 149–59.

18 Ward JD, Barnes CG, Fisher DJ, Jessop JD, Baker RWR. Improvement in nerve conduction following treatment in newly diagnosed diabetics. *Lancet* 1971; **i:** 428–31.

19 Preston FE, Ward JD, Marcola BH, Porter NR, Timperley WR, O'Malley BC. Elevated β-thromboglobulin levels and circulating platelet aggregates in diabetic microangiopathy. *Lancet* 1978; **i:** 238–40.

20 Rubenstein JJ, Pohost GM, Foster JR. The echocardiographic determination of isovolumic relaxation period in patients with normal and diseased coronary arteries (abstract). *Clin Res* 1973; **21:** 446.

21 DeMaria AN, Miller RR, Amsterdam EA, Markson W, Mason DT. Mitral valve early diastolic closing velocity in the echocardiogram: relation to sequential diastolic flow and ventricular compliance. *Am J Cardiol* 1976; **37:** 696–700.

22 Savage DD, Drayer JIM, Henry WL, *et al.* Echocardiographic assessment of cardiac anatomy and function in hypertensive subjects. *Circulation* 1979; **59:** 623–32.

23 Margolis JR, Kannel WB, Feinleib M, Dawber TR, McNamara PM. Clinical features of unrecognised myocardial infarction—silent and symptomatic. Eighteen year follow-up: the Framingham study. *Am J Cardiol* 1973; **32:** 1–7.

24 Boucher CA, Fallon JT, Johnson RA, Yurchak PM. Cardiomyopathic syndrome caused by coronary artery disease III, Prospective clinicopathological study of its prevalence among patients with clinically unexplained chronic heart failure. *Br Heart J* 1979; **41:** 613–20.

25 Kohner EM, Dollery CT. Diabetic retinopathy. In: Keen H, Jarrett J, eds. *Complications of diabetes* London: Edward Arnold, 1975: 7–98.

26 Thomsen AC. *The kidney in diabetes mellitus.* Copenhagen: Munksgaard, 1965.

27 Sharp CL, Butterfield WJH, Keen H. Diabetes survey in Bedford 1962. *Proc R Soc Med* 1964; **57:** 193–202.

28 Keen H, Rose GA, Pyke DA, Boyns D, Chlouverakis C, Mistry S. Blood-sugar and arterial disease. *Lancet* 1965; **ii:** 505–8.

29 *Coronary risk handbook.* New York: American Heart Association, 1973.

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Non-surgical extraction of a broken catheter sheath lodged in the right atrium, using a Dormia ureteral stone dislodger

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SUMMARY A broken Desillets Hoffman (DH) sheath which had lodged in the right atrium was extracted with the help of a Dormia ureteral stone dislodger. A critical appraisal of various non-surgical methods used so far to remove foreign bodies from the heart and great vessels is presented.

Intravascular catheterisation is widely practised in intensive care units and other hospital services as well as in the traditional cardiac catheterisation laboratories. Often foreign materials are left in the circulation at various points for a considerable length of time. Consequently the loss into the circulation of various fragments of catheters or ancillary materials (during placement or later) is being increasingly encountered. Removal is necessary in view of the dangers of septicaemia, arrhythmias, perforation, myocardial damage, thromboembolism, and sudden death (Harken and Zoll, 1946; Lassers and Pickering, 1967). Surgical retrieval of materials inside the heart carries a substantial risk of morbidity and perhaps even mortality. Various ingenious methods have, therefore, been used in an attempt to avoid thoracotomy for such iatrogenic complications. We report our experience with the retrieval of a Desillet Hoffman sheath from the right atrium and briefly appraise other methods.

Case report

A 22-year-old man was admitted to the cardiology service of the Nehru Hospital of this Institute for the investigation of repeated attacks of paroxysmal atrial tachycardia. The surface electrocardiogram showed type B WPW syndrome. In the course of percutaneous catheter placement for electrophysiological studies the entire body of a Desillets Hoffman (DH) sheath became detached from its head and lodged in the right atrium (Fig. 1). Attempts to remove it with various manoeuvres, including myocardial biopsy forceps, were unsuccessful. A Dormia ureteral stone dislodger was introduced

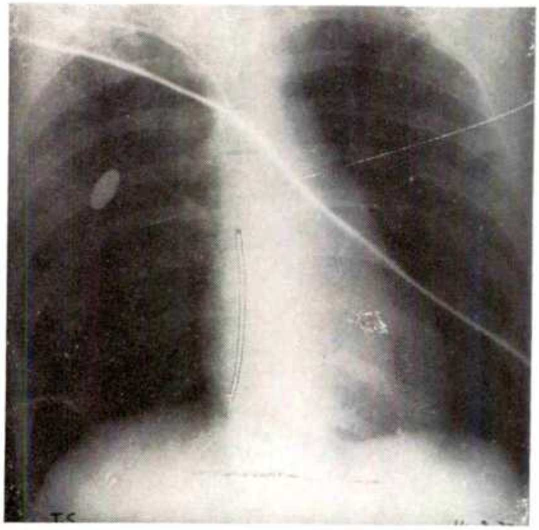

Fig. 1 *X-ray film of chest, anteroposterior view showing the Desillets Hoffman sheath in the right atrium. The outline of the sheath has been drawn in with a dotted line.*

through the right antecubital vein and advanced into the right atrium, and the sheath was entrapped in the basket and extracted.

Discussion

Non-surgical removal of a foreign body from the circulation was first reported by Thomas *et al.* (1964) who recovered the broken segment of a spring guide wire from the right atrium with a bronchoscopic forceps. Since then various devices have been used with some success.

GRASPING FORCEPS

Earlier reports advocated the use of bronchoscopic grasping forceps (Thomas *et al.*, 1964; Bloomfield, 1971). However, this technique is of limited use because grasping forceps are rigid and there is a danger of accidental perforation of blood vessels or cardiac chambers and damage to the valve apparatus. At present there is little support for the use of this instrument.

The use of a bioptome, often readily available in a cardiac catheterisation laboratory, has been advocated (Kurita *et al.*, 1972), but we found this of little value. The size and configuration of the grasping jaws clearly limits its usefulness, and the cutting edges may well bite through soft plastic materials.

LOOPSNARE CATHETERS

A doubled up guide wire inside a polythene catheter has been used to form a loop into which the foreign

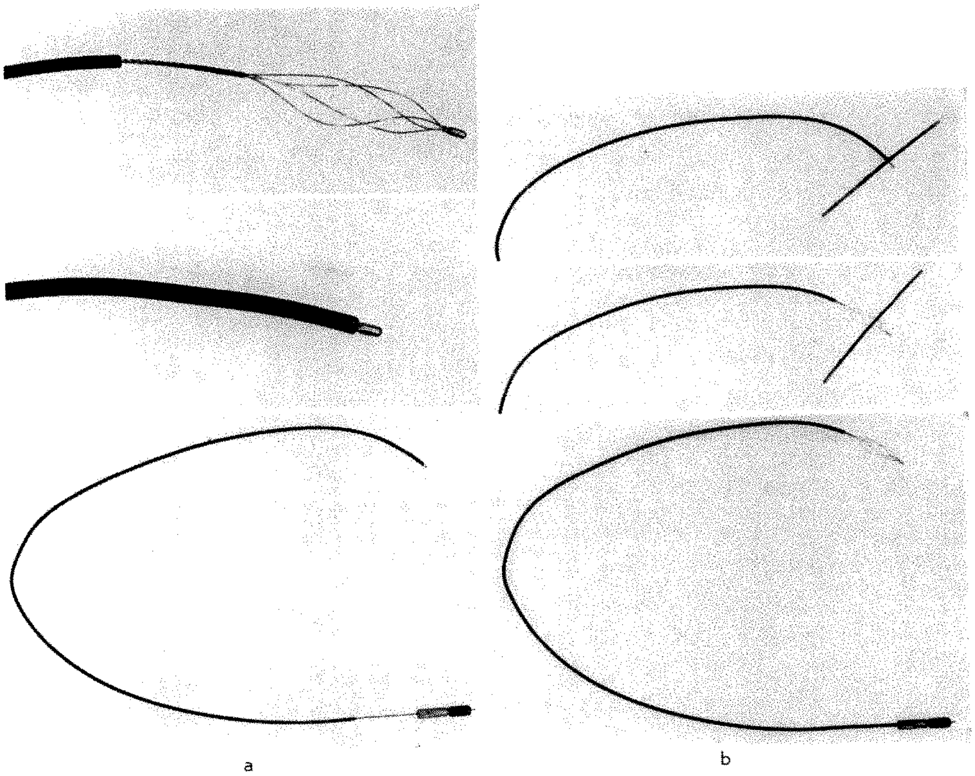

Fig. 2 (a) *The Dormia ureteral stone dislodger. Bottom row shows the complete catheter assembly. The middle row shows the closed end of the catheter at higher magnification. The top row shows the opened up strands of the basket when the metallic intruder is pushed out.* (b) *The Desillets Hoffman sheath retrieved from this patient is seen in a dummy operation within the closed catheter (top) and in the open basket (middle). The entire catheter assembly with open basket is shown at the bottom.*

body may be snared for removal (Massumi and Ross, 1967; Ramo *et al.*, 1968). The polythene catheter could be introduced percutaneously or through a cut down and advanced into the cardiac chambers or great vessels. Because of their encouraging results such catheters are now available commercially (Curry, 1969) though they can easily be designed from materials readily available in any cardiac catheterisation laboratory. Custom built designs can thus be fashioned. Even a flexible preformed hook-ended snare has been used in 2 cases (Rossi, 1970).

BASKET CATHETERS

Lassers and Pickering (1967) described the removal of a broken piece of guide wire from the aorta with the help of a Dormia ureteral stone dislodger introduced retrogradely from the femoral artery. There has been some concern at the possibility of perforation of the great vessels or the cardiac chambers by the hard tip of the Dormia catheter (Bloomfield, 1971; Block, 1973). Recently a similar catheter with a flexible filiform tip has been introduced (Drabinsky, 1976). Retrieval in our case was also possible with the Dormia catheter. When the inner steel core of the catheter (Fig. 2) is pushed out the helicoid strands open up into a basket cage into which the foreign body is carefully guided. Withdrawal of the basket into the lumen of the sheath closes the basket thus gripping the foreign body which is removed along with the catheter (Fig. 2). The fairly large size to which the basket opens would allow a large piece of catheter fragment to be removed. A Dotter retrieval set (Dotter *et al.*, 1971), which is a modification of the Dormia catheter, can be introduced percutaneously and is now available commercially. We feel that this should be stocked by all cardiac catheterisation laboratories.

Successful retrieval of foreign bodies from the right ventricle and pulmonary artery is reported with this catheter without any damage to valve apparatus and chordae tendineae (Dhingra *et al.*, 1973). Indeed, non-surgical retrieval appears to be possible and should be tried before surgical intervention is sought. There do not seem to be any published figures to allow one to estimate the percentage of failures when non-surgical techniques are used.

References

Block, P. C. (1973). Transvenous retrieval of foreign bodies in the cardiac circulation. *Journal of the American Medical Association*, **224,** 241-242.

Bloomfield, D. A. (1971). Techniques of nonsurgical retrieval of iatrogenic foreign bodies from the heart. *American Journal of Cardiology*, **27,** 538-544.

Curry, J. L. (1969). Recovery of a detached intravascular catheter or guide wire fragments. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, **105,** 894-896.

Dhingra, R. C., Rosen, K. M., and Rahimtoola, S. M. (1973). Transvenous removal of catheter fragments from the heart and pulmonary artery. *Archives of Internal Medicine*, **132,** 419-421.

Dotter, C. T., Rösch, J., and Bilbao, M. K. (1971). Transluminal extraction of catheter and guide wire fragments from the heart and great vessels; twenty nine collected cases. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, **111,** 467-472.

Drabinsky, M. (1976). Retrieval of embolized central venous catheter by a Dormia ureteral stone dislodger with straight filiform tip. *Chest*, **69,** 435- 437.

Harken, D. E., and Zoll, P. M. (1946). Foreign bodies in and in relation to the thoracic blood vessels and heart III. Indications for the removal of intracardiac foreign bodies and the behaviour of the heart during manipulation. *American Heart Journal*, **32,** 1-19.

Kurita, A., Kanazawa, M., Kanie, T., Kimura, E., Nakayama, K., and Shoji, T. (1972). Successful removal of a foreign body from the caval vein by use of endo-myocardial bioptome. *Japanese Heart Journal*, **13,** 464-469.

Lassers, B. W., and Pickering, D. (1967). Removal of an iatrogenic foreign body from the aorta by means of a ureteric stone catcher. *American Heart Journal*, **73,** 375-378.

Massumi, R. A., and Ross, A. M. (1967). Atraumatic, nonsurgical technic for removal of broken catheters from cardiac cavities. *New England Journal of Medicine*, **277,** 195-196.

Ramo, B. W., Peter, R. H., Kong, Y., and Morris, J. J., Jr (1968). Migration of a severed transvenous pacing catheter and its successful removal. *American Journal of Cardiology*, **22,** 880-884.

Rossi, P. (1970). Hook catheter technique for transfemoral removal of a foreign body from right side of the heart. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, **109,** 101-106.

Thomas, J., Sinclair-Smith, B., Bloomfield, D., and Davachi, A. (1964). Nonsurgical retrieval of a broken segment of steel spring guide from the right atrium and inferior vena cava. *Circulation*, **30,** 106-108.

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Primary pulmonary hypertension: effects of nifedipine

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SUMMARY The results of the medical treatment of primary pulmonary hypertension are usually very poor. A case of severe primary pulmonary hypertension in chronic heart failure was treated with the calcium antagonist nifedipine, a powerful vasodilator which acts directly on vascular smooth muscle. Nifedipine, administered in a dose of 20 mg sublingually, caused a pronounced fall in pulmonary and systemic vascular resistances (54 and 49%, respectively) and a rise in cardiac output (90·3%). Improvement was maintained over a three-month period. These data suggest that nifedipine can be used in the treatment of this condition.

Pulmonary arterial hypertension results from an increase in pulmonary blood flow, augmented resistance, or both. Primary pulmonary hypertension, a rare disease of unknown aetiology and with a progressive fatal course, is characterised by increased pulmonary vascular resistance. Previous experience with vasodilators[1–3] and subsequent morphometric studies[4] suggest that vasoconstriction is an important factor in the pathogenesis of the disease. The long-term treatment with the vasodilators used, however, gave poor results.[5 6] To test new vasodilator drugs in this condition therefore seems justified.

During the past few years, a new class of drugs has been introduced to treat cardiovascular disorders. These drugs have a common action on cellular membranes where they block the flow of calcium ions which takes place during the process of cellular excitation. We report our experience with one of these compounds, nifedipine, in the treatment of a patient with primary pulmonary hypertension.

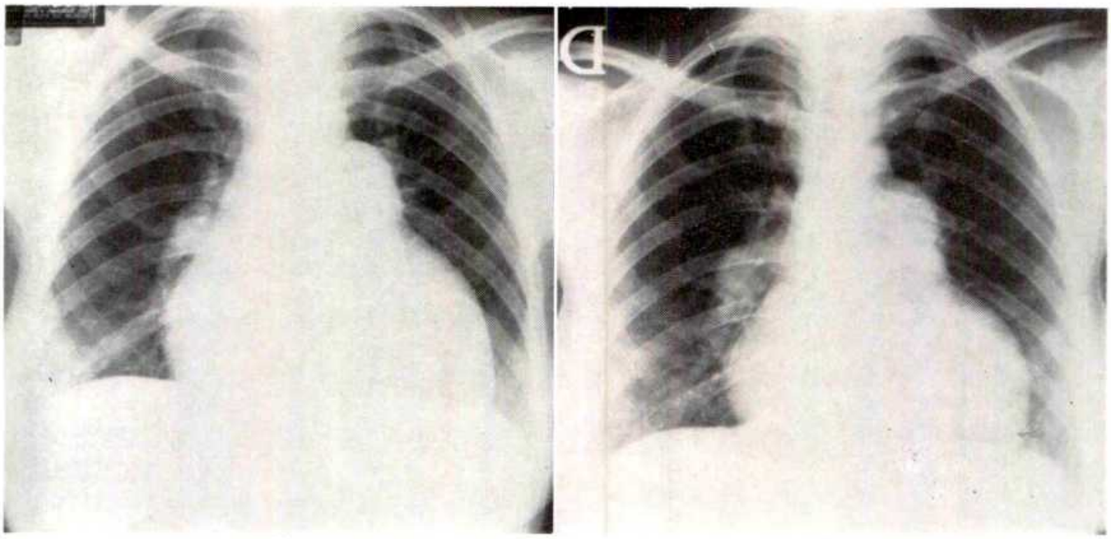
Case report

A 34-year-old married woman had suffered frequent episodes of bronchitis after her second pregnancy four years previously. One year later she had experienced syncope during effort. Right and left cardiac catheterisation, performed two months later, showed pulmonary arterial hypertension (pulmonary arterial pressure 65/25, mean 25 mmHg; pulmonary wedge pressure 12 mmHg; total pulmonary resistance 539 dynes s cm^{-5}; left ventricular systolic pressure 140 mmHg; left ventricular diastolic pressure 12 mmHg; cardiac output 3·56 l/min). No other abnormality was seen. Her condition slowly worsened, with progressive dyspnoea at rest and during effort, exertional syncope and cyanosis, abdominal pain, and ankle swelling.

In October 1978 the patient was admitted to our department. On examination she was cyanosed. The ankles were swollen and the jugular veins were engorged (venous pressure 10 cm above the sternal angle), with a predominant "a" wave. The pulse was small and the blood pressure was 90/50 mmHg. The liver was enlarged, tender, and actively pulsating. There was a sustained systolic lift in the third and fourth left intercostal spaces. On auscultation, a grade 3 pansystolic murmur, increasing on inspiration, was heard in the tricuspid area, the pulmonary component of the second sound was very loud, and a third heart sound was present. The electrocardiogram showed right axis deviation (mean QRS axis + 120°), right atrial enlargement, and right ventricular hypertrophy with right bundle-branch block. The echocardiogram suggested severe pulmonary hypertension with increased end-diastolic pressure and enlargement of the right ventricle. The chest *x*-ray film showed cardiomegaly with enlargement of the right atrium and ventricle, severe dilatation of the pulmonary artery, and poor vascularisation of the lung fields (Fig. 1).

She was treated with anticoagulants, digitalis, oxygen, and diuretics. While in hospital her condition worsened. In November 1978 the response to nifedipine was assessed; 20 mg was administered sublingually. Catheterisation showed a fall in total pulmonary resistance (mean fall 54%) and in systemic vascular resistance (mean fall 49%), with a slight decrease in mean pulmonary arterial pressure (mean decrease 14%) and a significant increase in cardiac output (mean increase 90·3%). These haemodynamic changes were evident 30 minutes after administration of the drug and reached maximum values at the third hour (Table 1, Fig. 2). Six days later the patient was tested with diazoxide. The injection of 180 and 300 mg of the drug in the pulmonary artery caused a fall in total pulmonary resistance (30 and 36%, respectively), while no reduction was observed with 45 mg of the drug and only a slight fall (18%) with a dose of 90 mg. Mean pulmonary arterial pressure was unchanged after the drug administration. Diazoxide 90, 180, and 300 mg caused an increase in cardiac output (23, 45, and 51%, respectively) and a fall in systemic vascular resistance (27, 29, and 40%, respectively). These changes were still evident one hour after the last injection of 300 mg diazoxide (Table 2). She began prolonged treatment with nifedipine 100 mg daily; the anticoagulants, digitalis, and diuretics were continued. Her dyspnoea at rest disappeared, dyspnoea on exertion and cyanosis decreased, the ankle oedema resolved, and she was able to lead a near normal life.

She was restudied after three months of treatment. Clinical examination showed slight pulmonary and tricuspid regurgitation and no signs of right heart failure. Chest *x*-ray film showed a reduction in the heart size (Fig. 1). Catheterisation, performed under basal conditions 12 hours after stopping the treatment, showed a reduction in pulmonary and systemic resistance and an increased cardiac output.



(a) (b)

Fig. 1 *Chest x-ray film before a and after b three months of treatment with nifedipine. A moderate decrease in heart size is seen.*

Table 1 *Haemodynamic changes after nifedipine (first study)*

	Heart rate (beats/min)	*Cardiac output (litres/min)*	*Pulmonary arterial pressure (mmHg)*			*Total pulmonary resistance (dynes s cm^{-5})*	*Systemic arterial pressure (mmHg)*			*Systemic vascular resistance (dynes s cm^{-5})*
			Syst	*Diast*	*Mean*		*Syst*	*Diast*	*Mean*	
Basal	88	2·23	94	51	63	2255	95	65	73	2615
30′	86	3·80	80	42	50	1050	85	60	64	1344
60′	78	3·42	80	44	54	1252	87	60	70	1624
120′	102	4·60	80	48	55	955	90	60	70	1215
180′	96	5·16	85	47	58	897	95	70	76	1176

Factor for converting mmHg to kPa is 0·133; factor for converting dynes s cm^{-5} to kPa s/l is 0·1.

The administration of nifedipine (20 mg sublingually) produced a distinct fall in total pulmonary and systemic vascular resistances (mean fall 39·9 and 26·5%, respectively) while cardiac output increased significantly (mean increase 33%). Mean pulmonary arterial pressure decreased (19·3%) but there was no reduction in mean systemic arterial pressure. In addition, during this test the maximum effect was observed between the second and third hours (Fig. 2, Table 3).

CATHETERISATION PROCEDURE

A number 7 Cournand catheter was inserted through an antecubital vein into the main trunk of the pulmonary artery and a polythene catheter was inserted into the femoral artery (Seldinger technique). Pulmonary and systemic arterial pressures were measured by Statham transducers. Cardiac output was determined by the Fick technique, using a three-minute collection of expired air. Measurements were repeated until a steady state

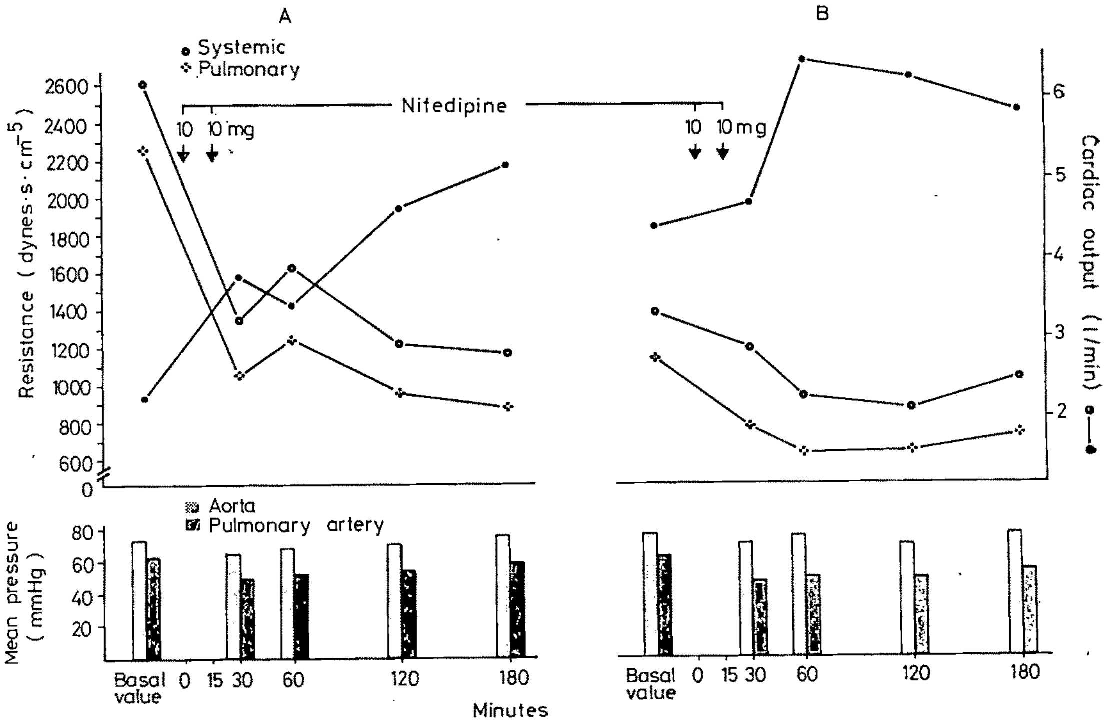


Fig. 2 *Haemodynamic changes after administration of nifedipine 20 mg.* (A) *first study;* (B) *second study (three months after treatment with nifedipine 100 mg daily).*

Table 2 *Haemodynamic changes after diazoxide*

	Heart rate (beats/min)	*Cardiac output (litres/min)*	*Pulmonary arterial pressure (mmHg)*			*Total pulmonary resistance (dynes s cm⁻⁵)*	*Systemic arterial pressure (mmHg)*			*Systemic vascular resistance (dynes s cm⁻⁵)*
			Syst	*Diast*	*Mean*		*Syst*	*Diast*	*Mean*	
Basal	75	2·63	86	45	54	1636	97	68	78	2364
45 mg	78	2·64	95	45	58	1755	96	65	72	2179
90 mg	78	3·24	98	45	54	1329	92	60	70	1722
180 mg	78	3·83	95	45	55	1144	100	64	80	1665
300 mg	78	3·98	90	38	52	1041	96	52	70	1402

Factor for converting mmHg to kPa is 0·133; factor for converting dynes s cm^{-5} to kPa s/l is 0·1.

Table 3 *Haemodynamic changes after nifedipine (second study)*

	Heart rate (beats/min)	*Cardiac output (litres/min)*	*Pulmonary arterial pressure (mmHg)*			*Total pulmonary resistance (dynes s cm^{-5})*	*Systemic arterial pressure (mmHg)*			*Systemic vascular resistance (dynes s cm^{-5})*
			Syst	*Diast*	*Mean*		*Syst*	*Diast*	*Mean*	
Basal	70	4·38	94	45	62	1139	109	62	76	1375
30′	70	4·67	72	32	46	786	100	53	70	1196
60′	73	6·44	76	37	50	620	100	57	75	930
120′	74	6·24	80	33	50	640	102	54	69	883
180′	73	5·84	80	35	54	738	113	62	76	1038

Factor for converting mmHg to kPa is 0·133; factor for converting dynes s cm^{-5} to kPa s/l is 0·1.

had been reached; the mean between the last two values was considered as basal. Pulmonary and systemic resistances were derived from the following formulae: $SVR = MAP \times 80/CO$, $TPR = MPAP \times 80/CO$, where SVR, systemic vascular resistances (dynes s cm^{-5}); MAP, mean arterial pressure (mmHg); CO, cardiac output (litres/min); TPR, total pulmonary resistances (dynes s cm^{-5}); MPAP, mean pulmonary arterial pressure (mmHg), and 80 is a factor for converting resistance units to dynes s cm^{-5}.

For technical reasons, it was impossible to measure the pulmonary capillary wedge pressure accurately.

Diazoxide test

After basal measurements, 45 mg diazoxide were injected rapidly into the pulmonary artery. Five minutes later all measurements were repeated. The same procedure was then repeated for successive injections of 90, 180, and 300 mg diazoxide.

Nifedipine test

Basal measurements were recorded; 10 mg nifedipine were then administered sublingually and again after another 15 minutes. All measurements were repeated 30, 60, 120, and 180 minutes after the first dose.

Discussion

The first reports on the acute effects of vasodilators in patients with primary pulmonary hypertension date to the early 'fifties. Dresdale *et al.*[7] and Gardiner[8] showed the efficacy of tolazoline in decreasing pulmonary vascular resistance in these patients, but oral treatment did not prove to be effective.[5 6] Other drugs with vasodilator action used in the treatment of primary pulmonary hypertension gave unsatisfactory results in most cases.[2 9 10]

Recently, the effect of the acute and chronic administration of diazoxide was studied in three patients with primary pulmonary hypertension[11]: haemodynamic and clinical improvement was observed in two. Diazoxide, on the other hand, was ineffective in a fourth patient whose pulmonary hypertension was probably of embolic origin.

During the past 10 years, several experimental studies have shown the distinct vasodilator effect of calcium antagonists. These compounds act directly on the smooth muscle cells with an inhibition of excitation contraction coupling and the consequent relaxation of variously induced contractures. This action is particularly effective on coronary, cerebral, and pulmonary arteries.[12] The pronounced vasodilator action of calcium antagonist drugs is the basis of the haemodynamic mechanism by which these substances exert their therapeutic action in angina pectoris.[13–15]

The action on peripheral resistance suggested also that these drugs may be useful in the treatment of systemic hypertension; in severe hypertension, Guazzi *et al.*[16] found nifedipine to be comparable to trimetaphan, nitroprusside, or diazoxide, drugs already used in the treatment of hypertensive emergencies.

The nifedipine mediated reduction in increased resistance accomplished through a direct action on vascular smooth muscle suggested that we should verify the effect of this drug in primary pulmonary hypertension. In the case studied, the acute administration of nifedipine sublingually produced a substantial fall in pulmonary and systemic resistances with a distinct increase in cardiac output. This was accompanied by a slight effect on pulmonary arterial pressure and no effect on systemic arterial pressure. The haemodynamic changes were already present at the first measurement 30 minutes after administration, and persisted for at least three hours (Table 1; Fig. 2).

Diazoxide administered acutely via the intravenous route was less effective: reduction in systemic and pulmonary resistances accompanied by an increase in cardiac output was appreciable only at the higher doses (180 and 300 mg), at which the systemic pressure was affected more than the pulmonary pressure.

Chronic treatment with nifedipine led to an important reduction in symptoms, with no episode of syncope and a pronounced reduction in dyspnoea; the signs of right heart failure diminished.

The clinical improvement was confirmed by the haemodynamic findings at catheterisation after three months of treatment with nifedipine. This procedure also showed that the acute administration of the drug was still capable of producing a pronounced haemodynamic effect (Fig. 2; Table 3).

At present, there are no other reported data on the use of calcium antagonists in the treatment of pulmonary hypertension, though in an experimental study McMurtry *et al.*[17] showed the efficacy of verapamil in relieving the pulmonary vasoconstriction induced by hypoxia in isolated rat lungs. These authors suggested that calcium antagonists might block an inward movement of calcium ions secondary to hypoxia, which may induce vasoconstriction. Our experimental data show that nifedipine is particularly effective in reducing the raised pulmonary resistance characteristic of primary pulmonary hypertension. Its prompt and prolonged action, together with the few reported side effects,[18] suggest the possibility of this drug being used in the chronic treatment of this disease.

However, in primary pulmonary hypertension the response to this, as well as to other vasodilators, can be extremely variable from time to time and from one subject to another,[2 9] probably in relation to the type and entity of pulmonary arterial changes.[19] Severe narrowing or obstructions of the pulmonary vessels caused by intimal fibrosis may substantially limit the vasodilator action of the drug, which should be most conspicuous when only vasoconstriction is present.

References

[1] Marshall RJ, Helmholz HF Jr, Shepherd JT. Effect of acetylcholine on pulmonary vascular resistance in a patient with idiopathic pulmonary hypertension. *Circulation* 1959; **20**: 391–5.

[2] Samet P, Bernstein W, Widrich J. Intracardiac infusion of acetylcholine in primary pulmonary hypertension. *Am Heart J* 1960; **60**: 433–9.

[3] Charms BL. Primary pulmonary hypertension: effect of unilateral pulmonary artery occlusion and infusion of acetylcholine. *Am J Cardiol* 1961; **8**: 94–9.

[4] Wagenvoort CA, Wagenvoort N. Primary pulmonary hypertension. A pathologic study of the lung vessels in 156 clinically diagnosed cases. *Circulation* 1970; **42**: 1163–84.

[5] Samet P, Bernstein W. Loss of reactivity of the pulmonary vascular bed in primary pulmonary hypertension. *Am Heart J* 1963; **66**: 197–9.

[6] Rao BNS, Moller JH, Edwards JE. Primary pulmonary hypertension in a child. Response to pharmacologic agents. *Circulation* 1969; **40**: 583–7.

[7] Dresdale DT, Michtom RJ, Schulz M. Recent studies in primary pulmonary hypertension including pharmacodynamic observations on pulmonary vascular resistance. *Bull NY Acad Med* 1954; **30**: 195–207.

[8] Gardiner JM. The effect of "Priscol" in pulmonary hypertension. *Australas Ann Med* 1954; **3**: 59–63.

[9] Daoud FS, Reeves JT, Kelly DB. Isoproterenol as a potential pulmonary vasodilator in primary pulmonary hypertension. *Am J Cardiol* 1978; **42**: 817–22.

[10] Seides SF, Kent KM, Rosing DR, Borer JS, Epstein SE. The effects of vasodilators on patients with pulmonary hypertension (abstract). *Circulation* 1978; **57** and **58**, suppl II: 81.

[11] Wang SWS, Pohl JEF, Rowlands DJ, Wade EG. Diazoxide in treatment of primary pulmonary hypertension. *Br Heart J* 1978; **40**: 572–4.

[12] Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. *Annu Rev Pharmacol Toxicol* 1977; **17**: 149–66.

[13] Hollman W, Rost R, Liesen H, Emirkanian O. The cardiopulmonary loading capacity in healthy persons and patients with coronary heart disease after application of Adalat. In: Lochner W, Braasch W, Kroneberg G, eds. *New therapy of ischemic heart disease.* Berlin: Springer-Verlag, 1975: 243.

[14] van den Brand M, Remme WJ, Meester GT, Tiggelaar-de Widt I, de Ruiter R, Hugenholtz PG. Changes in left and right ventricular haemodynamics in angina pectoris patients following Adalat administration. In: Jatene AD, Lichtlen PR, eds. *New therapy of ischemic heart disease.* Excerpta Medica International Congress series no. 388. Amsterdam: Excerpta Medica, 1976: 69–75.

[15] Lichtlen PR, Engel HJ, Amende I, Rafflenbeul W, Simon R. Mechanisms of various antianginal drugs. Relationship between regional flow behaviour and contractility. In: Jatene AD, Lichtlen PR, eds. *New therapy of ischemic heart disease.* Excerpta Medica International Congress series no. 388. Amsterdam: Exerpta Medica, 1976: 14–29.

[16] Guazzi M, Olivari MT, Polese A, Fiorentini C, Magrini F, Moruzzi P. Nifedipine, a new antihypertensive with rapid action. *Clin Pharmacol Ther* 1977; **22**: 528–33.

[17] McMurtry IF, Davidson AB, Reeves JT, Grover RF. Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs. *Circ Res* 1976; **38**: 99–104.

[18] Ebner F, Dünschede HB. Haemodynamics, therapeutic mechanism of action and clinical findings of Adalat use based on worldwide clinical trials. In: Jatene AD, Lichtlen PR, eds. *New therapy of ischemic heart disease.* Excerpta Medica International Congress series no. 388. Amsterdam: Excerpta Medica, 1976: 283–300.

[19] Wagenvoort CA, Wagenvoort N. *Pathology of pulmonary hypertension.* New York: John Wiley, 1977.

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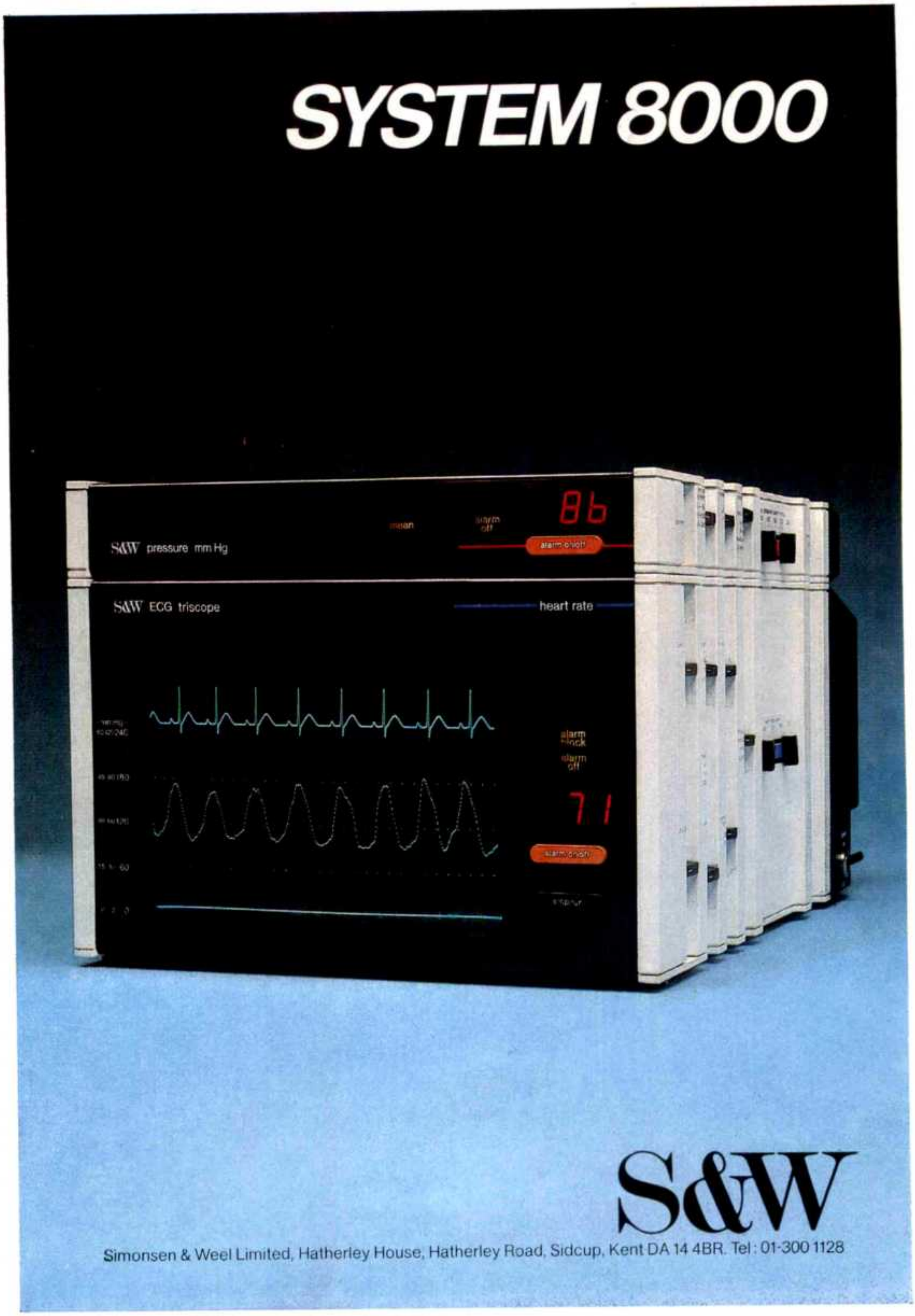

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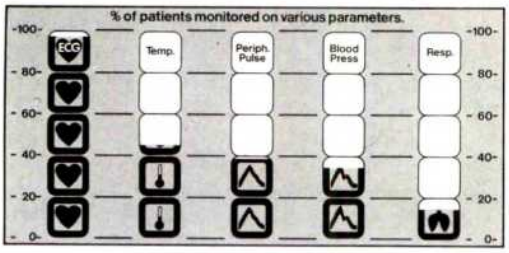

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by

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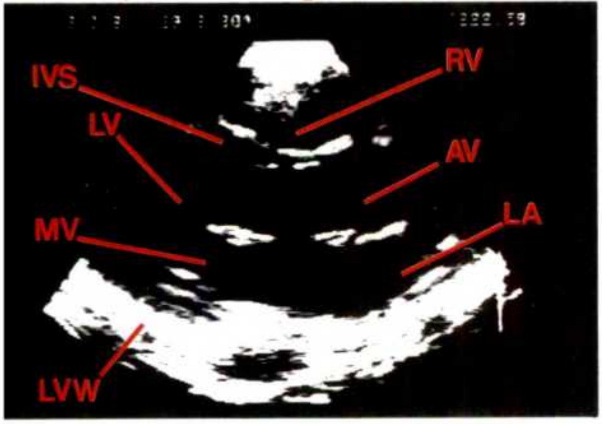

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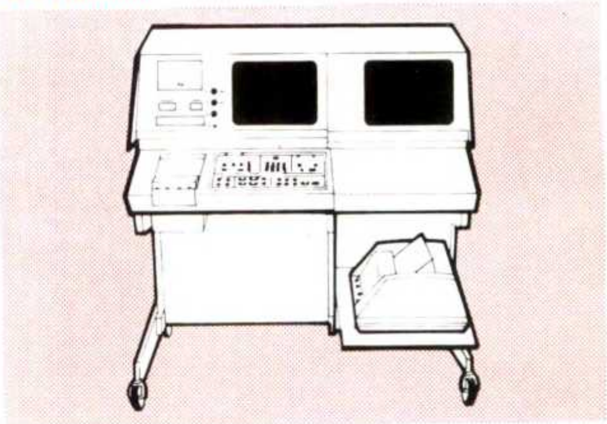

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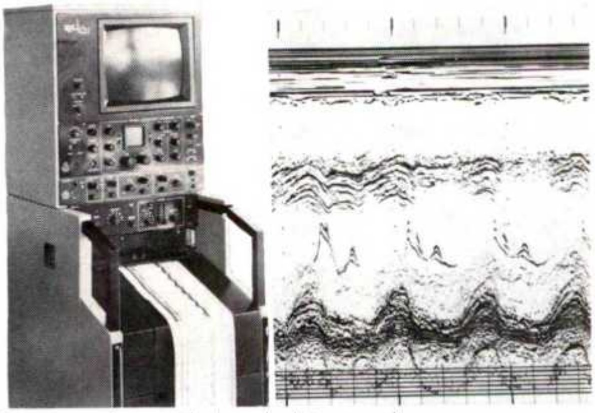

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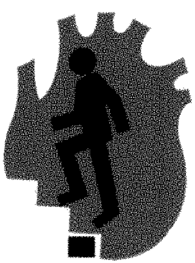

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References

1. Nayler, W.G. *Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
2. Flameng, W. *et al. Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
3. Detry, J.M.R. *et al. Eur. J. Cardiol.* **4,** 165, 1976.
4. Gobel, F.L. *et al. Am. J. Cardiol.* **37,** 139, 1976.
5. Jenkins, M.D. *et al. Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
6. Bloem, Th. J.J.M. *et al. Clin. Cardiol.* **2,** 407, 1979.
7. Shapiro, W. *Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
8. Nordstrom, L.A. *Chest,* **74,** 50, 1978.

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1	**Norway, Sweden and Finland 1968. 'Medical boards' recommendations on diet in the Scandinavian countries'.**	✓	**6**	**American Medical Association Council on Foods and Nutrition 1972. 'Diet and coronary heart disease'.**	✓
2	**USA Inter-Society Commission for Heart Disease Resources 1970. 'Primary prevention of atherosclerotic disease'.**	✓	**7**	**American Heart Association Committee on Nutrition 1973. 'Estimating the risk of coronary heart disease'.**	✓
3	**New Zealand Heart Foundation 1971. 'Coronary heart disease'.**	✓	**8**	**International Society of Cardiology 1973. 'Myocardial infarction. How to prevent. How to rehabilitate'.**	✓
4	**New Zealand Royal Society 1971. 'Coronary heart disease'.**		**9**	**Netherlands Nutrition Council 1973. 'Recommendations on the amount and nature of dietary fats'.**	✓
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11 Australian National Heart Foundation 1974. 'Dietary fat and coronary heart disease.'	✓	**16** Norwegian Ministry of Agriculture 1976. 'Nutrition and food policy.'	✓
12 United Kingdom D.H.S.S. (C.O.M.A.) 1974. 'Diet and coronary heart disease.'		**17** United Kingdom Royal College of Physicians and the British Cardiac Society 1976. 'Prevention of coronary heart disease.'	✓
13 Australian Academy of Science 1975. 'Report of a working group on diet and coronary heart disease.'	✓	**18** F.A.O./W.H.O. Expert Consultation 1977. 'Dietary fats and oils in human nutrition.'	✓
14 Germany (F.R.) Federal Health Report 1975. 'Edible fats and circulatory disorders.'	✓	**19** US Select Committee on Nutrition and Human Needs 1977. 'Dietary goals for the United States.'	✓
15 Canada Health and Welfare 1976. 'Diet and cardiovascular disease.'	✓	**20** European Society of Cardiology 1978. 'Preventing coronary heart disease.'	✓

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Br Heart J 1980; **44:** 357–60

Coronary patient—early treatment?

A A JENNIFER ADGEY

From the Regional Medical Cardiology Centre, Royal Victoria Hospital, Grosvenor Road, Belfast, N Ireland

There are some 150 000 deaths from coronary heart disease in the United Kingdom each year: 55 000 of these occur in people aged less than 70 years; approximately two-thirds take place outside hospital. The majority are sudden in that they happen within one hour of the onset of symptoms.

Nine out of every 10 early deaths from coronary artery disease are the result of ventricular fibrillation. Both clinical and experimental evidence indicates that after coronary occlusion the magnitude of the infarct is likely to be determined within the first few hours and may be influenced in a salutary way by early therapeutic intervention. The objectives therefore of prehospital coronary care are to attack the problem of sudden death outside hospital and to provide treatment for the patient with acute myocardial infarction at the earliest possible moment after the onset of symptoms.

In 1975 a Working Party of the Royal College of Physicians of London and the British Cardiac Society[1] stated that, "The Department of Health and Social Security (DHSS) and the Scottish Home and Health Department should actively encourage the development of mobile coronary care.... Doctor-manned mobile coronary care units should be developed wherever possible. In areas where this is not practicable a service manned by trained ambulancemen or other paramedical personnel should be developed.... A more positive approach to the problems of sudden unexpected death and to the high mortality in the first hours after a heart attack is necessary. More attention must be paid to the organisation of emergency medical services, including the provision of immediate coronary care.... Widespread instruction of the public in resuscitation should be encouraged as a further means of rescuing victims stricken by acute heart attacks. Such instruction could be carried out by trained laymen or medical personnel in schools, factories and large institutions."

These recommendations of the Working Party of the Royal College of Physicians and British Cardiac Society have been ignored by the authorities to whom they were directed. Though many hundreds of prehospital coronary care schemes operate in North America,[2] little or no attention has been paid in the UK to the emergency care of the coronary patient. The reason for this may relate to the policy of the DHSS.[3] That policy dictates that no further mobile coronary care units should be established in the United Kingdom since "no firm evidence has emerged that the use of specially equipped ambulances manned by ambulancemen who have received training in advanced techniques significantly affects the overall mortality rate of patients suffering from acute myocardial infarction". This policy has been instituted despite significant evidence in the United Kingdom from for example Belfast,[4] and Brighton,[5] and from the United States.[6] Using a rapid response system which serves a community of approximately 500 000 people over an area of 90 square miles, Cobb's unit in Seattle (L A Cobb, 1979, personal communication) resuscitated from ventricular fibrillation outside hospital 110 patients in 1977, and 95 patients in 1978, and discharged them home. If the annual heart disease mortality in Cobb's area of Seattle is similar to that quoted by Eisenberg *et al.*[7] and if recurrence of sudden death in the first year after resuscitation is allowed for, a reduction of 10 per cent in the community mortality in Seattle might be expected.

The policy of the DHSS appears to result from the improper assessment and a misunderstanding of the results of the studies in Bristol[8] and Nottingham,[9] both of which it financed. These studies purported to show that patients with myocardial infarction might be treated as successfully at home as in hospital. The earlier study, that carried out in Bristol,[8] was criticised because of the small number of patients randomised and because patients were randomised late after the onset of symptoms (median four hours[10]). The Nottingham studies have also been criticised. One of these was carried out over a four-year period and covered a population of approximately 100 000.[9] [11] In that area a doctor-manned mobile coronary care unit responded to calls from general practitioners to patients with suspected myocardial infarction. From the expected incidence of myocardial infarction,[12] some 1200 cases would have been anticipated in that population during the four years. Only 150 patients with a definite or probable myocardial infarction, however, were randomised to home or hospital treatment over this period. Thus, of the patients likely to have had a myocardial infarction over the period of study, only one in eight was randomised. From that study, Hill *et al.*[9] concluded that, "for the majority of patients to whom a general practitioner is called because of suspected infarction, hospital admission confers no clear advantage". Yet Colling and Dellipiani,[13] without any education of their public, indicated that a general practitioner was called to 50 per cent of cases with a suspected heart attack within an hour of the onset of symptoms in their community. It is of interest that in the Nottingham study[9] over 40 per cent of the patients with suspected myocardial infarction had contacted their doctor within one hour of the onset of symptoms and nearly 60 per cent within two hours. Nevertheless, the average time from the onset of symptoms to the arrival of the mobile team at the patient was three hours, and a further two hours elapsed before the randomisation was carried out.

In addition, in that study, Hill *et al.*[9] recorded that during the time between the patient's call for help and the arrival of the team, 14 patients had died, presumably suddenly. A further seven patients developed ventricular fibrillation after the arrival of the team; yet only three out of these survived six weeks. In contrast, 73 per cent of those patients who developed ventricular fibrillation outside hospital after the arrival of the Belfast mobile team survived to leave hospital. It has been made clear that the Nottingham patients, on admission to the coronary care unit, stay under the care of the general physician on duty that day.[11] The head of the unit considers his role to be that of an administrator and an educator.[11] The junior doctors manning the mobile coronary care unit are drawn from the general medical units of the hospital. This Nottingham experiment[9] showed no difference in the mortality between those managed at home and those in hospital when patients were seen late after the onset of symptoms. It has been suggested that the addition of a mobile coronary care unit to a hospital coronary care unit will reduce the cumulative mortality from myocardial infarction over a four-week period by 17 per cent (8% CCU, 9% mobile coronary care unit).[14] As has been confirmed in Nottingham, however, any reduction will be negligible unless early care is extended to the patient and it is both prompt and intensive.

In another Nottingham study, Hampton and Nicholas[15] carried out a randomised trial between a mobile coronary care unit manned by trained ambulancemen and a routine ambulance offering routine care. Pozen[16] commenting on this study stated that, "the one reported attempt at a randomised trial between mobile coronary care and routine ambulance care resulted in a skewed and uninterpretable data set". When the mobile coronary care unit was manned by trained ambulance personnel no patient became a long-term survivor from attempted resuscitation initiated outside hospital. Yet the authors concluded that, "until patients' behaviour patterns change, the only way the mobile coronary care unit concept can usefully be extended in this country is probably by equipping every ambulance that deals with emergencies with a defibrillator and training the crew to use it". Inconsistently a year previously Hampton *et al.*[17] stated that, "it is doubtful whether there would be any significant benefit from training ambulance crews to medical standards of drug administration and intubation".

The poor results of resuscitation from cardiac arrest outside the hospital in Nottingham are to be contrasted with more than 600 patients resuscitated from ventricular fibrillation outside hospital and discharged home in Seattle since 1970.[6] The Seattle system used trained paramedical personnel. In Brighton, Mackintosh *et al.*[5] reported that 40 patients were resuscitated from ventricular fibrillation outside hospital and were discharged home over a three-year period. Resuscitation was carried out by trained ambulance personnel.

The major question to be answered is not whether patients with coronary attacks should be managed at home or in hospital, but how the early high mortality from ventricular fibrillation can be reduced. Reduction in delay between the onset of symptoms and the call for help is clearly imperative. In order that this delay is reduced to a minimum, constant education of the public regarding the symptoms of the coronary attack is essential. It is also important that the public should receive training in cardiopulmonary resuscitation.[6] These educational programmes, however, must be supported by an emergency care system which delivers trained personnel and equipment rapidly to the scene. If such a system is not available patients will not call for help within the early minutes of the attack.

Mobile coronary care units manned by doctors or paramedical personnel have successfully resuscitated 8 to 44 per cent of patients from ventricular fibrillation outside hospital.[4 18 19] These figures, however, are still small. In order to increase these to 50 per cent or more, the equipment and trained personnel must be readily available where the patient collapses.

It has been estimated that the expected incidence of acute myocardial ischaemic attacks (including sudden deaths) is one or two cases per day per hundred thousand of the population.[20] In several areas throughout the United Kingdom interested general practitioners have for several years encouraged their patients to call for help immediately after the onset of symptoms. They have arranged that there is the minimum of delay between the time of the call for help and the arrival of a doctor with the patient[21] (and L C Cowley, 1979, personal communication). Several Health Centres are now fully equipped with a simple defibrillator and monitoring oscilloscope and the drugs required for the correction of arrhythmias. If defibrillators can be developed which sense ventricular fibrillation on paddle contact with the chest and only discharge a shock when ventricular fibrillation is present, then these instruments might even be available in homes of patients at risk, to be used by trained members of their family.

Summary and conclusions

While the negative attitude of the DHSS towards emergency coronary care in the UK continues, some 30 000 deaths from coronary artery disease occur annually outside hospital. The majority of premature deaths occur in middle-aged men of economic importance to the country and to their families. Coronary heart disease is the major cause of death in the Western world. The majority of deaths are sudden and result from ventricular fibrillation. Correction of ventricular fibrillation outside hospital is a practicable proposition. If the Seattle results were extrapolated to the UK, and allowing for the saving of lives in rural areas by trained general practitioners, then some 7500 lives might be saved annually in Great Britain.

References

1 Royal College of Physicians of London and the British Cardiac Society. The care of the patient with coronary heart disease: report of a joint working party. *J R Coll Physicians Lond* 1975; **10:** 5–45.

2 Sherman MA. Mobile intensive care units: an evaluation of effectiveness. *JAMA* 1979; **241:** 1899–901.

3 Department of Health and Social Security. Advanced training for ambulancemen, November 1976, Health notices *HN (76), 204.*

4 Adgey AAJ, Nelson PG, Scott ME, *et al.* Management of ventricular fibrillation outside hospital. *Lancet* 1969; **i:** 1169–71.

5 Mackintosh AF, Crabb ME, Grainger R, Williams JH, Chamberlain DA. The Brighton resuscitation ambulances: review of 40 consecutive survivors of out-of-hospital cardiac arrest. *Br Med J* 1978; **i:** 1115–8.

6 Thompson RG, Hallstrom AP, Cobb LA. Bystander-initiated cardiopulmonary resuscitation in the management of ventricular fibrillation. *Ann Intern Med* 1979; **90:** 737–40.

7 Eisenberg M, Bergner L, Hallstrom A. Paramedic programs and out-of-hospital cardiac arrest: II. Impact on community mortality. *Am J Public Health* 1979; **69:** 39–42.

8 Mather HG, Pearson NG, Read KLQ, *et al.* Acute myocardial infarction: home and hospital treatment. *Br Med J* 1971; **iii:** 334–8.

9 Hill JD, Hampton JR, Mitchell JRA. A randomised trial of home-versus-hospital management for patients with suspected myocardial infarction. *Lancet* 1978; **i:** 837–41.

10 Julian DG. What does intensive care achieve? In: Colling A, ed. *Coronary care in the community.* London: Croom Helm, 1977: 88–96.

11 Colling A, Carson P, Hampton J. Home or hospital care for coronary thrombosis? *Br Med J* 1978; **i:** 1254–9.

12 Colling A, Dellipiani AW, Donaldson RI, MacCormack P. Teesside coronary survey: an epidemiological study of acute attacks of myocardial infarction. *Br Med J* 1976; **ii:** 1169–72.

13 Colling A, Dellipiani A. A comparison of home and hospital care: the Teesside coronary survey. In: Colling A, ed. *Coronary care in the community.* London: Croom Helm, 1977: 38–72.

14 Acheson RM. The effectiveness of care of acute myocardial infarction: a review from the epidemiological viewpoint. In: Colling A, ed. *Coronary care in the community.* London: Croom Helm, 1977: 25–37.

15 Hampton JR, Nicholas C. Randomised trial of a mobile coronary care unit for emergency calls. *Br Med J* 1978; **i:** 1118–21.

16 Pozen MW. Pre-hospital coronary care: the current case for a paramedic strategy. *Am J Public Health* 1979; **69:** 13–4.

17 Hampton JR, Dowling M, Nicholas C. Comparison of results from a cardiac ambulance manned by medical or non-medical personnel. *Lancet* 1977; **i:** 526–9.

18 Criley JM, Lewis AJ, Ailshie GE. Mobile emergency care units: implementation and justification. *Adv Cardiol* 1975; **15:** 9–24.

19 Cobb LA, Baum RS, Alvarez H III, Schaffer WA. Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow-up. *Circulation* 1975; **51 & 52,** suppl III: 223–8.

20 Jones B. Large town with a district general hospital with a coronary care unit and mobile coronary care unit. In: Colling A, ed. *Coronary care in the community*. London: Croom Helm, 1977: 178–80.
21 Sproule BJ. General practitioners and coronary care (letter). *Br Med J* 1977; **i:** 289–90.

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Br Heart J 1980; **44:** 361–8

Cardiovascular complications of homozygous familial hypercholesterolaemia

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From the Departments of Clinical Cardiology and Diagnostic Radiology, Royal Postgraduate Medical School, and MRC Lipid Metabolism Unit, Hammersmith Hospital, London

SUMMARY Seven patients with homozygous familial hypercholesterolaemia, two female and five male, aged 12 to 25 years, underwent clinical and angiographic assessment to define the associated cardiovascular abnormalities. Four patients had angina, two of whom also had syncope on exertion. All had an ejection systolic murmur but no ejection click and a loud aortic second sound. All but one had a systolic gradient between the left ventricle and aorta, ranging from 20 to 80 mmHg at the time of presentation. Angiography showed a characteristic narrowing of the aortic root in all and five of the seven patients had coronary ostial stenosis. One patient died after an aortocoronary bypass and aortic valvotomy and two others underwent aortocoronary bypass and aortic valve replacement, one of whom also died after operation. The survivor and three other patients are now undergoing regular plasma exchange and remain well. The seventh patient died suddenly before the latter form of treatment could be started. These findings confirm that premature, severe atheroma of the aortic valve and root is a characteristic feature of homozygous familial hypercholesterolaemia and carries a high mortality.

Early death from the cardiac consequences of premature atheroma is the usual outcome of homozygous familial hypercholesterolaemia.[1 2] Inherited as an autosomal dominant, this rare disease is characterised by very high plasma levels of cholesterol[3] and the development of cutaneous and tendon xanthomata in childhood.[4] We have studied seven patients with this disorder, in whom we have been able to document both clinically and angiographically a characteristic distribution of atheroma in the aortic root and coronary arteries. The severity of symptoms in two patients warranted aortocoronary bypass and aortic valve replacement and a third underwent aortocoronary bypass with aortic valvotomy.

Case reports

CASE 1

P A-S (born 17 July 1953) was a 23-year-old Greek Cypriot student whose early history has been described previously.[5] Her parents were first cousins. Skin xanthomata had been noted at the age of 6 months but treatment for her hypercholesterolaemia was not started until the age of 9 years. She first attended this hospital at the age of 12 in 1966. At that time her serum cholesterol was above 26·0 mmol/l (1000 mg/dl) with a serum triglyceride of 0·50 mmol/l (45 mg/dl). She had bilateral corneal arcus and multiple xanthomata over elbows, knees, and ankles. Her arterial pulses were regular, but slow rising. Blood pressure 130/70 mmHg. She had a loud ejection systolic murmur in the aortic area.

In 1969, she developed typical angina. The electrocardiogram at this time showed sinus rhythm with left ventricular hypertrophy and widespread ST depression at rest. An exercise electrocardiogram was positive.

From 1969 to 1973, she received a variety of drugs (nicotinic acid, cholestyramine, Secholex, neomycin, clofibrate) which only partially controlled her hypercholesterolaemia. From 1974 she was treated by monthly plasma exchange.[5] At this time it was noted that she had a pronounced left ventricular heave and the aortic component of the second heart sound became palpable. She had a grade 3/4 ejection systolic murmur in the aortic area with a thrill but no ejection click.

In 1976 she underwent cardiac catheterisation and a pressure gradient of 75 mmHg was recorded across the aortic valve. Angiography showed a normally contracting left ventricle, but the aortic

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root showed gross irregularity with ostial narrowing of the left coronary artery (see Fig. 1).

By February 1977 her angina had become more severe, with episodes of chest pain at rest, and she was admitted for cardiac surgery. At operation the aortic root was seen to be small with extensive mural atheroma. The aortic valve had soft mobile cusps which were somewhat thickened and were fused at one commissure. When this was divided the aortic valve orifice seemed adequate. Both coronary ostia were very stenosed. Three grafts were inserted between the aorta and the anterior descending and circumflex branches of the left coronary artery, and the right coronary artery. She came off bypass easily but died on the second postoperative day from intraperitoneal haemorrhage.

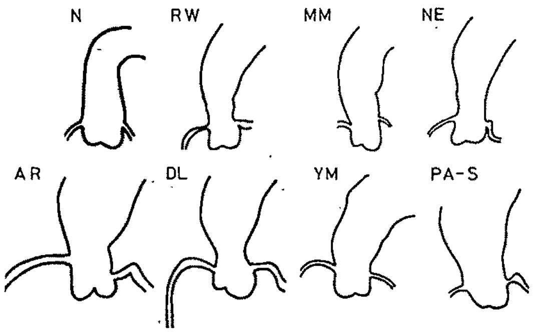

Fig. 1 *Line drawings of aortograms of all patients are shown in comparison with the normal (N). The aorta normally expands in diameter as it reaches the aortic valve. In all seven homozygotes, aortography showed a characteristic irregular narrowing of the proximal aorta. This funnelling appears to be a distinctive feature of this disease.*

CASE 2

Y M was a 23-year-old Zambian Asian (born 18 July 1952) whose parents were also first cousins and whose family tree is shown below (Fig. 2). The symbol □ represents normal subjects; ◩, and ◑ heterozygotes; and ■, and ● homozygotes: values of serum cholesterol concentration are also shown.

Achilles tendon xanthomata were first noted at the age of 5 in 1957 and he subsequently developed xanthomata over the elbows. In 1969 he was started on cholestyramine and clofibrate in an attempt to lower his serum cholesterol but with little obvious benefit. At the age of 20 in 1972, he developed angina on exertion.

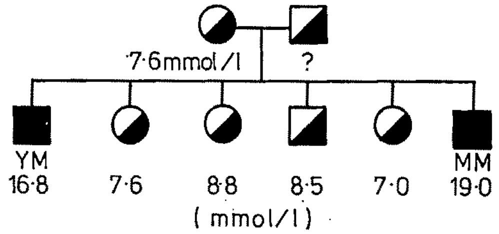

Fig. 2 *Family tree of YM (case 2) and of MM (case 3).*

On examination he had bilateral corneal arcus and multiple large cutaneous and tendinous xanthomata. His pulse was 72 and regular. He had a wide pulse pressure, blood pressure 180/100 mmHg. There was an obvious ejection systolic murmur and early diastolic murmur in the aortic area. Chest *x*-ray was normal. Electrocardiography showed sinus rhythm and pronounced left ventricular hypertrophy. The serum cholesterol was 16·8 mmol/l (689 mg/dl).

In July 1974, cardiac catheterisation (at The London Hospital) demonstrated a gradient across the valve of 30 mmHg. Aortography showed irregular funnelling of the aorta down to the valve (Fig. 1) with some aortic regurgitation. Coronary angiography showed diffuse disease of the left anterior descending and circumflex arteries, together with severe narrowing at the origin and in the first centimetre of the right coronary artery.

In December 1975, the patient was referred by Professor R Cohen for consideration for plasma exchange but died suddenly, aged 23, before this could be instituted.

CASE 3

M M is the 15-year-old youngest brother of case 2 (Y M) (see family tree, Fig. 2); at the age of 5 years he had skin lesions similar to those of his brother. In 1976, when he was 12, he first attended this hospital. Examination disclosed early corneal arcus and widespread cutaneous planar and tendinous xathomata. His pulse was regular and normal in character, blood pressure 110/70 mmHg, but he had bilateral carotid and femoral bruits. The aortic component of the second sound was loud and he had a grade 3/4 ejection systolic murmur in the aortic area. Chest *x*-ray was normal, electrocardiography did not show any abnormalities, but echocardiography did disclose a thickened and narrowed aortic root. His serum cholesterol was 19·0 mmol/l (735 mg/dl), triglyceride 0·9 mmol/l (80 mg/dl).

In January 1978, angiography confirmed that the aortic root was narrowed and irregular (Fig. 1) though cardiac catheterisation disclosed no gradient across the valve or supravalvular area. Coronary angiography showed a stricture in the proximal third of the left anterior descending artery (Fig. 3) but there were no ostial stenoses.

He is now undergoing regular plasma exchange. He has remained well and has not developed any cardiovascular symptoms.

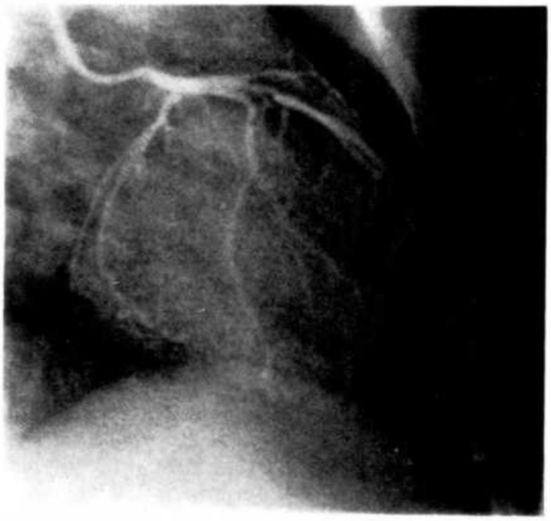

Fig. 3 *Left coronary angiogram of MM (case 3) showing a long stricture at the origin of the left anterior descending artery. The distal vessels are unaffected.*

CASE 4

A R was born on 17 November 1950 of an English father and Greek mother. Tendon xanthomata were first noticed at the age of 12 years. In 1970 at the age of 19 her serum cholesterol was 15·6 mmol/l (600 mg/dl), triglyceride 2·2 mmol/l (194 mg/dl). Examination showed no corneal arcus but she had multiple tendon xanthomata. Her pulse rate was 80 per minute and of normal character, blood pressure 115/75 mmHg. She had bruits over the carotid arteries and in the aortic area, and a grade 2/4 ejection systolic murmur. Chest *x*-ray and electrocardiogram were normal.

She received various cholesterol-lowering drugs over the next five years but without much success. She then underwent a trial of plasma exchange[5] but this was abandoned after a year because of difficulty of venous access.

In 1975, she developed angina on exertion. Examination of the cardiovascular system disclosed no new signs. Resting and exercise electrocardiograms were normal. Cardiac catheterisation showed a gradient across the aortic valve of 34 mmHg. Angiography showed narrowing and irregularity of the aortic root. The left coronary ostium also was narrowed.

In 1976, a portacaval shunt was carried out, as previously described,[6] but unfortunately this procedure resulted in only a temporary fall in serum cholesterol (see Fig. 4). In December 1978, she developed severe central chest pain and syncopal attacks on exertion. Examination showed a change in the character of her pulse, which was now very slow in rising. Blood pressure was 110/70 mmHg. There was an obvious left ventricular heave, a grade 3/4 aortic systolic murmur, and the aortic component of the second sound was loud. Electrocardiogram showed obvious left ventricular hypertrophy and an exercise electrocardiogram was strongly positive. Repeat catheterisation now showed a pressure gradient across the valve of 130 mmHg and on angiography the left ventricle was very hypertrophied.

She underwent cardiopulmonary bypass in February 1979. At operation patchy atheroma was seen in the ascending aorta but the sinuses of Valsalva had been virtually obliterated by large atheromatous cushions. The aortic valve was excised and the aortic root reconstructed with a Dacron graft to allow placement of a 23 mm Björk-Shiley valve. Three aortocoronary bypass grafts were inserted to the left anterior descending, circumflex, and right coronary arteries.

After successful treatment of postoperative bacterial endocarditis the patient is now remarkably well and is undergoing regular plasma exchange via an arteriovenous fistula in the arm.

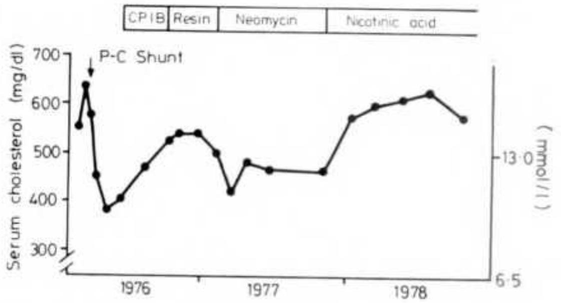

Fig. 4 *Serial cholesterol levels in the patient A R (case 4) after a portacaval shunt (PC shunt).*

CASE 5

R W, a 23-year-old Englishman (born 21 March 1953), was first noticed to have xanthomata at the age of 5 years. His family tree is shown in Fig. 5. He was initially treated with conventional cholesterol-lowering drugs (nicotinic acid, clofibrate, and cholestyramine) by Dr E Jepson who subsequently referred him for plasma exchange in October 1975.

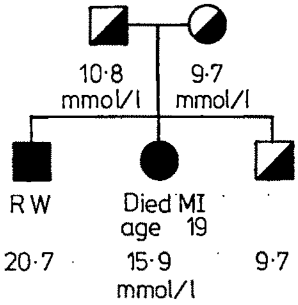

Fig. 5 *Family tree of RW (case 5).*

Examination showed bilateral corneal arcus and multiple cutaneous and tendon xanthomata. He had bruits over the carotid and femoral arteries; blood pressure 125/70 mmHg. There was a grade 3/4 ejection systolic murmur and the aortic component of the second sound was loud. Serum cholesterol was 20·7 mmol/l (795 mg/dl) and triglyceride 0·9 mmol/l (78 mg/dl). Chest *x*-ray was normal and electrocardiogram showed sinus rhythm and evidence of a previous anteroseptal infarct, with Q waves from V1 to V4. An exercise electrocardiogram was negative.

Cardiac catheterisation showed a gradient across the aortic valve of 40 mmHg. Angiography showed some apical dyskinesia and the aortic root was narrowed and deformed with gross irregularity (Fig. 1). Coronary angiography demonstrated two small strictures in the left main stem and one in the right coronary ostium.

The patient was started on plasma exchange in 1977 and he has remained well.[7]

CASE 6

D L is a 16-year-old English boy who presented with xanthomata around the elbows and heels at the age of 9 years. His family history is shown below (Fig. 6). He was treated for four years by conventional cholesterol-lowering agents and during this time his serum cholesterol fluctuated around 15·6 mmol/l (600 mg/dl).

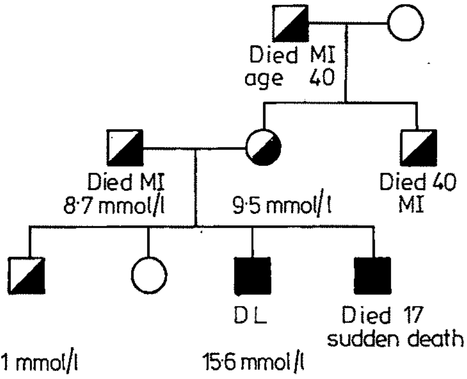

Fig. 6 *Family tree of DL (case 6).*

He was referred to this hospital by Dr J Hall when he was 12 years old for consideration for plasma exchange. Examination disclosed bilateral corneal arcus and multiple cutaneous and tendon xanthomata. Pulse was of normal character, blood pressure 130/70 mmHg. He had no carotid bruits, but there was a loud ejection systolic murmur in the aortic area and a loud aortic component of the second sound. Chest *x*-ray, electrocardiogram, and exercise electrocardiogram were all normal, but echocardiography showed a thickened and narrowed aortic root (Fig. 7). His serum cholesterol was 20·6 mmol/l (780 mg/dl) and triglyceride 1·1 mmol/l (97 mg/dl).

Cardiac catheterisation showed a pressure gradient across the aortic valve of 20 mmHg. Angiography demonstrated funnelling and narrowing of the aortic root (Fig. 1). Both coronary ostia were narrowed.

Regular plasma exchange was started in 1976 and two cardiac catheterisations at annual intervals have shown the pressure gradient across the valve to be unchanged, as described elsewhere.[7]

CASE 7

N E was a 19-year-old English student. Xanthomata were noted at the age of 18 months and by 7½ years (1968) he had extensive xanthomata and had developed angina. He was treated with clofibrate and cholestyramine but his serum cholesterol levels remained persistently raised between 17·6 mmol/l (675 mg/dl) and 25·2 mmol/l (975 mg/dl). In 1976 he developed syncopal attacks and a 24 hour electrocardiographic tape recording showed periods

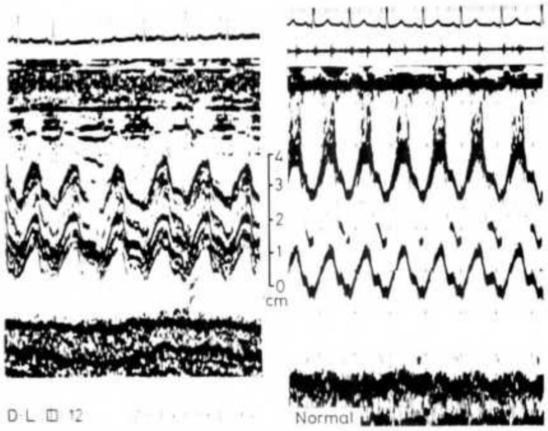

Fig. 7 *Echocardiography of patient D L (case 6) in comparison with a normal child of the same age shows narrowing and apparent thickening of the aortic root and valve cusps. In addition there are many abnormal echoes within the aortic root suggesting distorted movement of the cusps.*

of sinus arrest, atrioventricular dissociation, and ischaemic ST changes. A pacemaker was implanted at St Mary's Hospital, London.

In April 1979, he was referred by Professor V Wynn for consideration for plasma exchange. He complained of increasing angina on exertion, and had continued to suffer syncopal attacks. Examination disclosed bilateral arcus, xanthelasma, and some xanthomata. His pulse was 72 and slow rising, blood pressure 100/60 mmHg. He had bilateral carotid thrills and bruits. The apex beat showed a distinct left ventricular heave. There was a systolic thrill over the praecordium and a grade 3/4 ejection systolic murmur. The aortic component of the second sound was very loud. Electrocardiogram showed demand pacing but the unpaced beats showed distinct left ventricular hypertrophy.

Cardiac catheterisation showed a gradient across the aortic valve of 80 mmHg. Angiography indicated hypertrophy of the left ventricle. The aortic root showed widespread atheromatous deposits causing considerable narrowing and funnelling (Fig. 1 and 8) Coronary angiography showed strictures of the left anterior descending artery and proximal third of the right coronary artery. In June 1979, a Konno operation[8] was carried out to widen the aortic root, and a 25 mm Björk-Shiley valve and three aortocoronary bypass grafts were inserted. Postoperative progress was complicated by bacterial endocarditis, and development of an aorto-right ventricular fistula. He subsequently underwent a further operation to close the fistula; he died during the operation.

Discussion

Homozygous familial hypercholesterolaemia is a rare disorder,[9] the estimated incidence in Western countries being less than 1:1 000 000. There have been a number of case series previously published[10 11] but in none of these have the characteristic cardiovascular complications of the disease been fully documented. Though aortic stenosis has been recognised clinically and at necropsy,[12–14] it is only in recent years that angiographic study of patients has been performed and described, and then only in isolated instances. The abnormalities which have been reported in individual cases include strictures of the coronary arteries,[1] aortic stenosis, and narrowing of the aortic root.[15–17]

We have been able to study seven patients with homozygous familial hypercholesterolaemia. All were submitted at least once to cardiac catheterisation and angiography in order to define precisely the cardiac abnormalities.

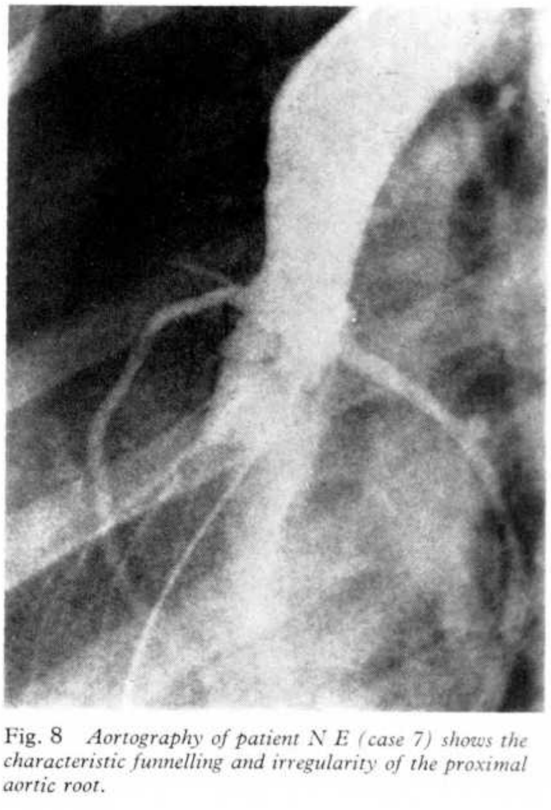

Fig. 8 *Aortography of patient N E (case 7) shows the characteristic funnelling and irregularity of the proximal aortic root.*

Three of the seven patients had no symptoms of cardiovascular involvement. The remaining four all suffered from typical angina. Two of them also had syncopal attacks on exertion.

All the patients had a loud ejection systolic murmur in the aortic area, a well recognised clinical finding.[12–16] In addition, each had a characteristic loud closure sound of the aortic valve. None had an ejection click.

Electrocardiography showed an old anterior infarct in one patient (R W, case 5); a further four patients had or developed evidence of left ventricular hypertrophy. Three patients (M M, case 3; D L, case 6, and N E, case 7) were examined by echocardiography. In each of the three, the aortic root was shown to be narrowed and apparently thickened and the aortic valve movement was distorted.

Aortography provides the best means of recognising the typical cardiovascular features of this disease. In all patients the proximal aortic root was narrowed and its outline was irregular and funnelled towards the aortic valve (Fig. 1 and 8). This represents the accumulation of atheroma which is most noticeable in the sinuses of Valsalva and extends proximally to involve the coronary ostia and aortic valve cusps. Strictures were commonly seen in the proximal portions of the coronary arteries (Fig. 3) but the distal vessels were remarkably free of disease. Catheterisation across the aortic valve recorded systolic pressure gradients ranging from nil in M M (case 3) to 130 mmHg in A R (case 4).

Pressure gradients between the left ventricle and aorta have been described in previous case reports,[13 16] but Wennevold and Jacobsen[16] considered that the gradient in their patient was the result of the supravalvular narrowing. In all our patients the gradient was at valve level and no gradient could be shown above that site. The appearance of the supravalvular part of the aorta in our patients was similar to that described by Wennevold and Jacobsen[16] and it seems unlikely that such a long but relatively slight degree of narrowing could be responsible for gradients of 95 mm which they observed. The aortic valve presumably cannot open fully because of atheromatous masses occupying the sinuses of Valsalva and it may be these rather than atheromatous deposits on the cusps themselves which determine the obstruction.

The three patients without angina were found at cardiac catheterisation to have the lowest gradients across the aortic valve (Table), whereas the two patients with both angina and syncope had the highest gradients. It is noteworthy that case 4 was studied twice during the period 1975 to 1978 during which her serum cholesterol was poorly controlled (Fig. 4). Over these three years, the gradient across the aortic valve increased from 34 mmHg to 130 mmHg, her angina became more severe, and she developed the ominous symptom of syncope.

The loud closure sound of the aortic valve in homozygous familial hypercholesterolaemia presumably results from atheromatous involvement of the aortic cusps. The ejection systolic murmur probably represents turbulent flow through the narrowed aortic valve orifice as well as across the irregular and narrowed aortic root (Fig. 1 and 8). An ejection click is not heard but the loud aortic closure sound is characteristic. It is important to recognise aortic stenosis but its severity is difficult to assess clinically. The character of the carotid pulses may be altered as a result of atheromatous deposits within them and the form of the peripheral pulses may be modified by inelasticity of the large conducting arteries for the same reason. The aortic murmur may be lengthened by turbulence within the aortic root and murmurs over the carotids may arise locally so that the murmur may be no guide to the severity of obstruction to left ventricular outflow. Left ventricular hypertrophy may be recognised by palpation and electrocardiography but

Table *Summary of initial cardiovascular findings in homozygotes*

Case no.	*Patient*	*Sex*	*Age when studied (y)*	*Angina*	*Syncope*	*Systolic murmur (grade)*	*Loud A_2*	*ECG*	*LV aortic systolic pressure gradient (mmHg)*
1	P A-S	F	23	+	−	3/4	+	LVH	75
2	Y M	M	22	+	−	2/4	+	LVH	30
3	M M	M	14	−	−	3/4	+	Normal	0
4	A R	F	25	+	−	2/4	+	Normal	34
5	R W	M	22	−	−	3/4	+	Q waves, V1–V4	40
6	D L	M	12	−	−	2/4	+	Normal	20
7	N E	M	19	+	+	3/4	+	LVH	80

an atrial beat and ST-T wave changes may equally result from associated coronary ostial involvement. Narrowing of the aortic root and apparent thickening can be shown by echocardiography, but multiple echoes from within the aortic box make assessment of the size of the aortic valve orifice difficult. Measurement of the left ventricular-aortic gradient remains essential and the rapid increase in severity as in case 4 underlines the need for serial measurements in these patients.[7] The progression of aortic stenosis was heralded by worsening angina and the onset of syncopal attacks in our patients. These may lead to sudden death unless surgical relief is obtained; the surgery is complex and the operative risks are high. There is, however, now some evidence which suggests that effective control of the serum cholesterol by plasma exchange may prevent or delay the development of these complications.[7]

Maximal deposition of atheroma in the proximal part of the aorta is the reverse of the usual situation[14] and is a unique feature of homozygous familial hypercholesterolaemia. Experimentally, lesions very similar to those found in homozygotes have been induced in rats made hypercholesterolaemic by diet.[18] Studies in pigs and dogs[19] suggest that transendothelial flux of lipoproteins would be greatest in areas of greatest sheer stress, these being the sinuses of Valsalva, coronary ostia, and ascending aorta. Under normal circumstances, however, these regions are relatively free from atheroma possibly because efflux as well as influx of lipoproteins is thought to be promoted by high sheer stresses occurring at the arterial wall.[20] Superimposition of extreme hypercholesterolaemia upon a normal haemodynamic background might be expected to enhance influx of lipoprotein cholesterol without necessarily promoting efflux. If so this could explain the premature onset and unusual anatomical localisation of atheroma in homozygous familial hypercholesterolaemia.

We are grateful to Dr E Jepson and Professor V Wynn for allowing us to include the patients R W and N E, respectively. These patients were studied at this hospital but remained primarily under their care.

References

1 Bialostozky D, Luengo M, Magos C, Zorrilla E. Coronary insufficiency in children. *Am J Cardiol* 1975; **36:** 509–14.

2 Rigdon RH, Willeford G. Sudden death during childhood with xanthoma tuberosum: review of literature and report of a case. *JAMA* 1950; **142:** 1262–71.

3 Fredrickson DS, Levy RI. Familial hyperlipoproteinemia. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. *The metabolic basis of inherited disease.* New York: McGraw Hill, 1972: 545–614.

4 Khachadurian AK. The inheritance of essential familial hypercholesterolemia. *Am J Med* 1964; **37:** 402–7.

5 Thompson GR, Lowenthal R, Myant NB. Plasma exchange in the management of homozygous familial hypercholesterolaemia. *Lancet* 1975; **i:** 1208–11.

6 Soutar AK, Myant NB, Thompson GR. Simultaneous measurement of apolipoprotein B turnover in very low and low density lipoproteins in familial hypercholesterolaemia. *Atherosclerosis* 1977; **28:** 247–56.

7 Thompson GR, Myant NB, Kilpatrick D, Oakley CM, Raphael MJ, Steiner RE. Assessment of long-term plasma exchange for familial hypercholesterolaemia. *Br Heart J* 1980; **43:** 680–8.

8 Konno S, Imai Y, Iida Y, Nakajima M, Tatsuno K. A new method for prosthetic valve replacement in congenital aortic stenosis associated with hypoplasia of the aortic valve ring. *J Thorac Cardiovasc Surg* 1975; **70:** 909–17.

9 Thompson GR. Familial hypercholesterolaemia. In: Peeters H, ed. *Lipoprotein molecule.* Nato Advanced Study Institute Series. Series A: Life sciences, Vol. 15, Plenum Press, New York 1978; 215–26.

10 Brown MS, Goldstein ML. Familial hypercholesterolemia: genetic, biochemical and pathophysiologic considerations. *Adv Intern Med* 1975; **20:** 273–96.

11 Mabuchi H, Tatami R, Haba T, *et al.* Homozygous familial hypercholesterolemia in Japan. *Am J Med* 1978; **65:** 290–7.

12 Cook CD, Smith HL, Giesen CW, Berdez GL. Xanthoma tuberosum, aortic stenosis, coronary sclerosis and angina pectoris. Report of a case in a boy 13 years of age. *Am J Dis Child* 1947; **73:** 326–33.

13 Barr DP, Rothbard S, Eder HA. Atherosclerosis and aortic stenosis in hypercholesteremic xanthomatosis. *JAMA* 1954; **156:** 943–7.

14 Roberts WC, Ferrans VS, Levy RI, Fredrickson DS. Cardiovascular pathology in hyperlipoproteinemia. *Am J Cardiol* 1973; **31:** 557–70.

15 Stanley P, Chartrand C, Davignon A. Acquired aortic stenosis in a 12 year old girl with xanthomatosis. *N Engl J Med* 1965; **273:** 1378–80.

16 Wennevold A, Jacobsen JG. Acquired supravalvular aortic stenosis in familial hypercholesterolemia. *Am J Med* 1971; **50:** 823–7.

17 Berger GMB, Miller JL, Bonnici F, Joffe HS, Dubovsky DW. Continuous flow plasma exchange in the treatment of homozygous familial hypercholesterolemia. *Am J Med* 1978; **65:** 243–51.

18 Záhör Z, Czabonová V. Experimental atherosclerosis of the heart valves in rats following a long-term atherogenic regimen. *Atherosclerosis* 1977; **27:** 49–57.

19 Fry DL. Responses of the arterial wall to certain physical factors. In: Ciba Foundation Symposium 12 (New Series). *Atherogenesis: initiating factors.* Amsterdam: Associated Scientific Publishers, 1973; 93–125.

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Br Heart J 1980; **44:** 369–80

Assessment of prognostic factors in patients undergoing surgery for non-rheumatic mitral regurgitation

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SUMMARY Twenty-four patients who had undergone mitral valve surgery for pure non-rheumatic mitral regurgitation were studied non-invasively six months to six years postoperatively. The long-term results of operation were assessed on the basis of clinical history, echocardiography, and treadmill stress testing using a points scoring system. The score so obtained was used to divide the patients into those with a good response to surgery (group 1) and those responding poorly (group 2). The effects on the long-term surgical outcome of several intraoperative and preoperative factors were then analysed both together and separately.

A short symptomatic history (<1 year), a normal left ventricular end-diastolic volume index ($\leqslant 100$ ml per m^2), and a large post-ectopic potentiation of KV max (>50 s^{-1}) were found to be favourable prognostic factors when analysed independently. An angiographic ejection fraction $<0{\cdot}5$ was uniformly associated with a poor outcome, and 71 per cent of patients in atrial fibrillation at the time of operation also responded badly. In those patients with good long-term function, cold potassium cardioplegia was more commonly used than intermittent aortic cross clamping as the means of intraoperative myocardial preservation, though this difference did not reach conventional significance.

A standard analysis of variance allowed assessment of length of history, left ventricular end-diastolic volume index, and type of valve prosthesis simultaneously. This indicated that both length of history and left ventricular end-diastolic volume index were highly significant prognostic factors. The use of a Björk-Shiley as opposed to a Starr-Edwards prosthesis also emerged as significantly favouring a good long-term result.

The state of the left ventricular myocardium before operation and the type of valve prosthesis used were thus shown to be the prime determinants of surgical outcome in these patients. The optimum time for operation was shown to be within one year of the onset of symptoms, and before the left left ventricular end-diastolic volume index exceeds 100 ml per m^2, or the ejection fraction falls to $<0{\cdot}5$. At such a time, irreversible changes in myocardial function sufficient to negate the beneficial effects of mitral valve surgery have not yet occurred.

The overall mortality and long-term functional capacity after mitral valve replacement have improved considerably since the operation was first performed successfully in 1960.[1] Operative mortality has fallen from 18 per cent[2] to 2 to 5 per cent, with a late mortality of 10 to 16 per cent.[3 4] In this hospital, the 30 day mortality for all patients undergoing mitral valve replacement averaged 7·2 per cent from 1976 to 1978, the period during which the majority of patients in the present study underwent operation. This improvement in mortality has been the result in the main of advances in intraoperative factors—principally surgical techniques, methods of myocardial preservation, and prosthetic valve design. Mitral valve replacement for pure mitral regurgitation, however, has been substantially less successful than for pure mitral stenosis—20 per cent versus 5 per cent early mortality.[5] The poor results in these patients are associated with low cardiac output states postoperatively—almost invariably in those with long-

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standing preoperative congestive heart failure and impaired left ventricular function at the time of operation.

Two differing views have been forwarded to explain these unsatisfactory results. Kirklin[6] has pointed out that the timing of operation depends upon the relative risks of the uncorrected disease versus those of operation and prosthesis combined. The poor outcome of operation until recently has meant that operation has usually been delayed until symptoms were far advanced and refractory to medical treatment. At this stage, impairment of cardiac functional reserve resulting from long-standing regurgitation results in the myocardium being unable to compensate for the increased afterload which accompanies the sudden return of valvular competence by mitral valve replacement. In Kirklin's view, since prognosis is now less influenced by surgical factors, operation ought to be advised earlier as its delay merely results in further myocardial impairment so contributing to operative mortality and chronic incapacity. The alternative view is that the events of prime prognostic importance occur during operation, not before it.[7] Thus further improvement in results would be principally dependent upon advances in methods of intraoperative myocardial preservation and valve design.

The purpose of the present study was to assess the influence of (a) intraoperative factors, and (b) the preoperative functional status of the left ventricle as determined by clinical, haemodynamic, and angiographic indices on the long-term surgical outcome of a group of patients with pure non-rheumatic mitral regurgitation. On the basis of the preoperative indices an attempt was made to define criteria which would indicate the optimum time for surgery in such patients.

Subjects and methods

The study group consisted of 24 patients (15 men and nine women) who had survived mitral valve surgery for pure non-rheumatic mitral regurgitation and who consented to further investigation (Table 1). All patients were operated on from 1973 to 1978 and in all cases at least six months and no more than six years had elapsed since operation. A further six patients who fulfilled the inclusion criteria either could not be contacted or refused consent.

All 24 patients had undergone cardiac catheterisation and data from left ventriculography were available in 20 of these. Patients with mitral stenosis or more than trivial disease of other valves were excluded, as were those with clinical or angiographic evidence of coronary artery disease preoperatively. In fact, 16 of the 24 patients had undergone selective coronary angiography and in these no critical lesions (>50% of the luminal diameter) were demonstrated. In the eight patients who did not have coronary angiography, the absence of coronary artery disease was not proven but was assumed on the basis of (i) lack of relevant symptoms and signs either preoperatively or between operation and restudy in all patients, and (ii) lack of wall motion abnormalities on left ventriculography in the four patients who had left ventriculography but not coronary angiography.

All patients underwent non-invasive assessment consisting of the following:

(a) *Clinical history and examination*—particular attention being paid to symptomatology (New York Heart Association Classification: NYHA) and the degree of subjective improvement since operation. Clinical evidence of prosthetic valve dysfunction or paraprosthetic leak was sought.

(b) *M-mode echocardiography*—scanning was

Table 1 *Operative data and aetiology*

	Age at operation (mean ±SEM)	*Mean time since opn. (mth) (±SEM)*	*Aetiology*			*Operative procedure*			*Mean total bypass time (min) (±SEM)*	*Duration of ischaemia (min) (mean ±SEM)*	*Intermittent aortic occlusion*	*Cold K^+ cardioplegia*
			FVS	*IRCT*	*SBE*	*B-S*	*S-E*	*Other*				
Group 1 (n=10)	56·9 ±3·9	30·4 ±5·4	7	2	1	7	1	1× xenograft	107·1 ±8·7	68·1 ±7·0	2	8
Group 2 (n=14)	57·2 ±2·0	44·2 ±4·7	11 (8)	2	1 (1)	4	8	1×L-K 1× McGoon repair	98·8 ±8·8	46·1 ±4·2	9	5
Total (n=24)	57·1 ±2·0	39·5 ±3·1	18 (13)	4	2 (2)	11	9	4			11	13

FVS, Floppy valve syndrome; IRCT, idiopathic rupture of chordae tendineae; SBE, subacute bacterial endocarditis; B-S, Björk-Shiley prosthesis; S-E, Starr-Edwards prosthesis; L-K, Lillehei-Kaster prosthesis; SEM, standard error of the mean.
Figures in parentheses refer to the number of patients with ruptured chordae secondary to other pathology.

carried out using a Smith-Kline Ekoline 20 ultrasonoscope with a 2·25 MHz focused transducer. Records were made on photographic paper at speeds of 25 to 100 mm/s. Echoes from the left side of the interventricular septum and the posterior left ventricular endocardium were first identified with the transducer angled caudally and laterally to a position just below the prosthetic valve echo. In this position, the internal diameter of the left ventricle was measured at the instant of peak inward motion of the posterior wall (systole, LVIDs) and at the electrocardiographic Q wave (diastole, LVIDd). The fractional shortening per cent (FS %) and the mean velocity of circumferential fibre shortening (mean V_{CF}) were derived from the following formulae:

$$\text{FS }\% = \frac{\text{LVIDd} - \text{LVIDs}}{\text{LVIDd}} \times 100$$

$$\text{and mean } V_{CF} = \frac{\text{LVIDd} - \text{LVIDs}}{\text{LVIDd} \times \text{ET}}$$

where ET is the ejection time in seconds. This was taken as the interval between echocardiographic aortic valve opening and closure. If adequate aortic valve echoes were not observed, then ejection time was measured as the time from onset to peak posterior left ventricular wall motion.[8]

The motion of the prosthetic valve and of the septum was noted and the presence of clot formation sought in order to assess prosthetic valve function and the presence or absence of paraprosthetic leak.[9]

(c) *Maximal exercise stress testing*—this was performed on an Avionics E16 programmable treadmill. The standard Bruce procedure of continuous three minute exercise stages was carried out and maximal exercise performance was encouraged by adopting a symptomatic end-point of chest pain, dyspnoea, or fatigue. The electrocardiogram was continuously monitored on an Avionics Exerstress 3000 electrocardiograph system and nine lead printout (the six limb leads + V4 to 6) obtained towards the end of each stage. The time-into-procedure achieved was noted and the functional aerobic impairment calculated from a standard nomogram. Maximal heart rate and systolic blood pressure were noted but not incorporated into the functional grading system (see below).

GRADING OF POSTOPERATIVE FUNCTIONAL STATUS

Since no single index of myocardial function is valid under all circumstances,[10] a scoring system based on improvement in symptoms (change in NYHA class), echocardiographic measurements (mean V_{CF} and FS %), and the results of exercise testing (time-into-procedure; and functional aerobic impairment) was devised. Table 2 indicates the values for each of the five variables which were taken to indicate normal (score 1), mildly impaired (score 2), or grossly impaired (score 3) results. The final score reflecting functional status at restudy was obtained by adding up the individual scores for all five variables. For most analyses we considered the patients in two groups: group 1 (total score $\leqslant 8$) with good functional capacity indicating a satisfactory response to surgery and group 2 (total score $\geqslant 9$) with impaired functional status in keeping with an unsatisfactory outcome.

Table 2 *Criteria underlying functional grading of postoperative status*

	Functional score		
	1	*2*	*3*
NYHA classification	*Improvement by two classes or to Class 1*	*Improvement by one class*	*No change in class*
Fractional shortening (%)	$\geqslant 25$	15–24	$\leqslant 14$
Mean circumferential shortening velocity (circ/s)	$\geqslant 0.9$	0·6–0·8	$\leqslant 0.5$
Time-into-procedure (min)	$\geqslant 7.5$	4·5–7·4	$\leqslant 4.4$
Functional aerobic impairment (%)	$\leqslant 13$	14–26	$\geqslant 27$

Group 1 (good functional status) = total score $\leqslant 8$.
Group 2 (poor functional status) = total score $\geqslant 9$.

ASSESSMENT OF PREOPERATIVE STATUS

Data were obtained from each patient's hospital records, operation notes, and cardiac catheterisation report. The following were considered.

(a) *Clinical*—NYHA grading of dyspnoea; the duration of dyspnoea; and the preoperative cardiac rhythm.

(b) *Haemodynamic*—the maximum and minimum values of the first derivative of the high fidelity Telco or Millar micromanometer pressure recordings (max and min dP/dt) obtained by electrical differentiation. These were noted at rest and after an ectopic beat.

—The maximum velocity of contractile element shortening × a stiffness constant (KV max).

The values at rest and after an ectopic beat were derived using the micromanometer tracings from a plot of

$$\log \frac{\text{d Developed pressure}}{\text{dt}}$$

against pressure,[11] by an electronic processor.[12] The post-ectopic potentiation was calculated by subtraction.

—Cardiac index (CI) calculated as

$$\frac{\text{cardiac output (green dye)}}{\text{body surface area}}$$

—Stroke volume index (SVI) calculated as

$$\frac{\text{CI}}{\text{heart rate}}$$

—Pulmonary vascular resistance (PVR) calculated as:

$$\frac{\text{Mean pulmonary artery pressure} - \text{mean wedge pressure}}{\text{Cardiac output (green dye)}}$$

(c) *Angiographic*—the left ventricular cineangiogram in the right anterior oblique projection was used for analysis. A computerised light pen system enabled the left ventricular end-diastolic volume index, stroke volume index, ejection fraction (EF), and peak V_{CF} to be derived. The percentage regurgitant volume (% RV) was calculated as:

$$\frac{\text{angiographic cardiac output} - \text{green dye cardiac output}}{\text{angiographic cardiac output}} \times 100$$

OPERATIVE DETAILS (Table 1)

Mitral regurgitation was corrected surgically by McGoon mitral valve repair in one patient (case 21), while the remaining 23 patients had mitral valve replacement. Of these, 11 had Björk-Shiley disc prostheses, nine had Starr-Edwards (models 6320 and 6400 ball and cage prostheses), and three had other types of artificial valve (detailed in Table 1). The choice of prosthetic valve type was based on the surgical preference current at that time and no selection on the basis of preoperative left ventricular function, left ventricular dimension, or severity of mitral regurgitation was made.

With a single exception, the type of intraoperative myocardial preservation used fell into one of two regimens—either (i) mild systemic hypothermia (30 to 32°C) with intermittent aortic cross-clamping to produce ischaemic arrest (11 cases), or (ii) mild systemic hypothermia with cold potassium cardioplegia using St. Thomas' Hospital solution (1 litre of 4°C Ringer's solution containing 16 mmol potassium chloride, 16 mmol magnesium chloride, and 1 mmol procaine) infused into the aortic root below the clamp over two to three minutes (13 cases). With this regimen topical profound cardiac cooling was used by running Hartmann's solution at 4°C through the pericardium. The one exception (case 9) had cold cardioplegia in an identical manner, but with coronary infusion of ordinary 4°C Ringer's solution in place of St. Thomas' Hospital solution.

Statistical analysis

Initially the results were analysed by Student's t test (paired when appropriate) for small sample sizes or by χ^2 test with Yates' correction for small samples. Analysis of individual factors in this way, however, does not take into account the effect of interaction between the different indices. In order to do this, the functional score was used as the "response" variable and a standard analysis of variance approach[13] adopted. This was effected by means of a "generalised linear model" fitting program called GLIM available on the University of London computer. This program, however, assumes that the scores have an underlying Gaussian distribution. Since such an assumption is not necessarily valid, the response variable was turned into a dichotomy by dividing the results into two groups (group 1 with a good response and group 2 with a poor response to surgery). In view of the relatively small numbers of patients in the study such a dichotomy resulted in there being insufficient data to analyse more than three factors simultaneously.

In the GLIM program a model incorporating the chosen factors is fitted to the given data. Each factor is then excluded in turn and any worsening of the fit between the remaining model and the data is assessed. In this way, the effect of each factor may be analysed having allowed for all others.

To obtain maximum information the results were analysed by all three approaches.

Results

The clinical, echocardiographic, and stress test results are shown in Table 3, together with the appropriate functional score for each index. Group 1 consists of those patients with a total score $\leqslant 8$ and represents a good response to operation. Group 2 patients had a total score $\geqslant 9$ indicating poor postoperative functional status. In none of the patients studied was there clinical or echocardiographic evidence of prosthetic valve dysfunction, clot formation, or paraprosthetic leak.

The results are presented in three sections. In section A statistical analysis is by standard χ^2 and t tests; in section B analysis is by GLIM on the ungrouped data; and in section C by GLIM on the dichotomised data.

SECTION A

(1) Clinical data

(a) Symptomatology: all 24 patients studied were symptomatic when operated on, 13 having Class II (NYHA) dyspnoea and 11 Class III preoperatively. The degree of symptoms and limitation of physical working capacity as judged by the NYHA classification were similar in the two groups. This index was hence not predictive of surgical response for an individual or either group as a whole. After operation, seven patients (29%) failed to improve their grading at all—the remaining 17 (71%) improving by at least one grade. Three patients (12·8%) improved by two clinical grades.

(b) Atrial fibrillation: 12 out of 17 patients (71%) with atrial fibrillation at the time of operation responded poorly (group 2) whereas of the patients in sinus rhythm only two out of seven (29%) did badly. Though this difference did not reach conventional significance ($p > 0{\cdot}1$) a trend was apparent (see section B).

(c) Restudy interval: the mean time between operation and restudy for all patients was 39·5 ±3·1 months. There was no significant difference ($p > 0{\cdot}05$) between the mean for group 1 (30·4 ±5·4 months) and that for group 2 (44·2 ±4·7 months).

(d) Age at operation: the age range was from 29 to 71 years (mean 57·1 ±2·0 years) with the majority in their early 60s. No significant difference ($p > 0{\cdot}1$) between the mean ages for group 1 (56·9 ±3·9 years) and group 2 (57·2 ±2·0 years) was found.

(2) Length of history (Fig. 1)

The duration of the presenting symptoms varied considerably from two months to 16 years. The mean for all 24 patients was 32·0 months ±8·7. In group 1 the mean duration of symptoms before operation was 10·2 ±12·3 months which was significantly shorter ($p < 0{\cdot}05$) than for group 2 (47·6 ±10·4). Fig. 1 also shows that eight out of 10 (80%) patients in group 1 had symptomatic histories shorter than one year while 11 out of 14 (79%) of group 2 complained of symptoms for one year or more before surgery.

(3) Left ventricular end-diastolic volume index (Fig. 2)

The mean left ventricular end-diastolic volume index (ml/m^2) (calculated as left ventricular end-diastolic volume ml/body surface area m^2) for group 1 was 94·1 ±12·2 ml/m^2 and that for group 2 was 146·4 ± 11·1 ml/m^2. The difference was highly significant ($p < 0{\cdot}01$). In addition, Fig. 2 indicates that seven out of nine (78%) group 1 patients on whom angiographic data were available had an index of 100 ml/

Table 3 *Postoperative clinical, exercise, and echocardiographic data*

Case no.	*Clinical (NYHA) grade*			*Postop exercise test*				*Postop echocardiogram*				*Total score*
	Preop	*Postop*	*Score*	*Time-into-procedure (min)*		*FAI (%)*		*Percentage fract. short.*		*Mean V_{CF}*		
Group 1:												
1	III	II	(2)	6	(2)	−25	(1)	37	(1)	1·4	(1)	7
2	II	I	(1)	10	(1)	− 8	(1)	30	(1)	1·2	(1)	5
3	III	I	(1)	9	(1)	− 5	(1)	25	(1)	0·9	(1)	5
4	III	II	(2)	8	(1)	0	(1)	15	(2)	0·6	(2)	8
5	III	I	(1)	5	(2)	6	(1)	17	(2)	0·7	(2)	8
6	II	I	(1)	9	(1)	− 8	(1)	20	(2)	0·8	(2)	7
7	III	II	(2)	6·5	(2)	5	(1)	28	(1)	0·9	(1)	7
8	II	I	(1)	7	(2)	14	(2)	23	(2)	1·0	(1)	8
9	II	I	(1)	6·5	(2)	6	(1)	26	(1)	1·1	(1)	6
10	II	I	(1)	6·5	(2)	10	(1)	22	(2)	0·8	(2)	8
Group 2:												
11	II	I	(1)	7	(2)	10	(1)	14	(3)	0·6	(2)	9
12	II	II	(3)	3	(3)	60	(3)	6	(3)	0·2	(3)	15
13	II	II	(3)	6	(2)	10	(1)	24	(2)	1·0	(1)	9
14	II	I	(1)	6	(2)	20	(2)	14	(3)	1·1	(1)	9
15	III	I	(1)	7	(2)	0	(1)	15	(2)	0·5	(3)	9
16	III	II	(2)	6	(2)	16	(2)	19	(2)	0·7	(2)	10
17	II	II	(3)	3	(3)		(3)	14	(3)	0·6	(2)	14
18	III	II	(2)	6	(2)	20	(2)	16	(2)	0·7	(2)	10
19	III	II	(2)	6	(2)	12	(1)	24	(2)	0·7	(2)	9
20	III	III	(3)	3	(3)	40	(3)	19	(2)	0·7	(2)	13
21	II	II	(3)	4	(3)	21	(2)	16	(2)	0·6	(2)	12
22	II	I	(1)	7	(2)	5	(1)	13	(3)	0·5	(3)	10
23	III	III	(3)	4	(3)	18	(2)	20	(2)	0·8	(2)	12
24	II	II	(3)	3	(3)	68	(3)	30	(1)	1·3	(1)	11

Figures in parentheses represent the functional score for individual variables.
Case 21 underwent mitral valve repair—all others had mitral valve replacement.

m^2 or less. In contrast, all 11 patients (100%) with angiographic data in group 2 had an index exceeding 100 ml/m^2.

(4) Combination of left ventricular end-diastolic volume index and length of history (Fig. 3)
The combination of an index equal to or larger than 100 ml/m^2 and a length of history greater than one year (the critical values differentiating group 1 from group 2) defined a subgroup of nine patients all of whom responded poorly to surgery. This combination of critical variables thus proved a highly specific predictor of unsatisfactory surgical response.

(5) Other angiographic variables
(a) Ejection fraction: the mean preoperative ejection fraction did not differ significantly ($p > 0 \cdot 1$) between group 1 ($0 \cdot 65 \pm 0 \cdot 04$) and group 2 ($0 \cdot 55 \pm 0 \cdot 05$) (Fig. 4). Of interest, however, was the finding that all three patients with an ejection fraction $< 0 \cdot 5$ responded poorly to surgery. In group 1 the mean

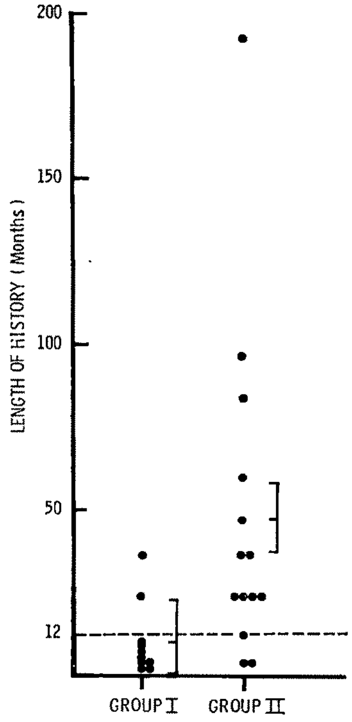

Fig. 1 *Duration of symptomatic history according to satisfactory (group 1) or unsatisfactory (group 2) functional capacity at follow-up. The means and standard errors of the means are displayed and the critical time of one year indicated. (See text.)*

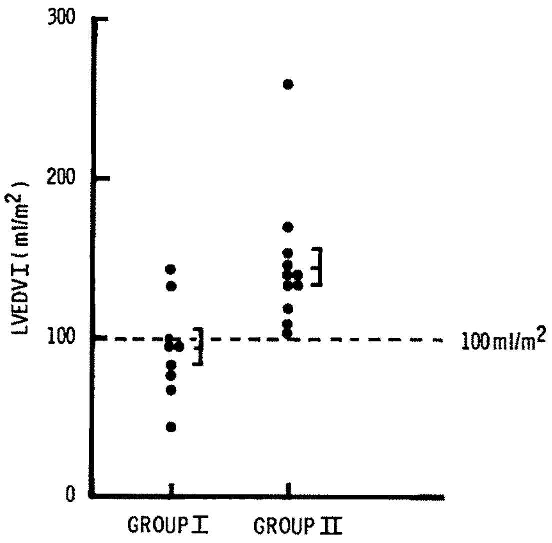

Fig. 2 *Comparison between left ventricular end-diastolic volume index (LVEDVI) in those patients responding well (group 1) and those responding poorly (group 2) to mitral valve surgery. The critical left ventricular end-diastolic volume index (100 ml/m²), group means, and SEMs are indicated.*

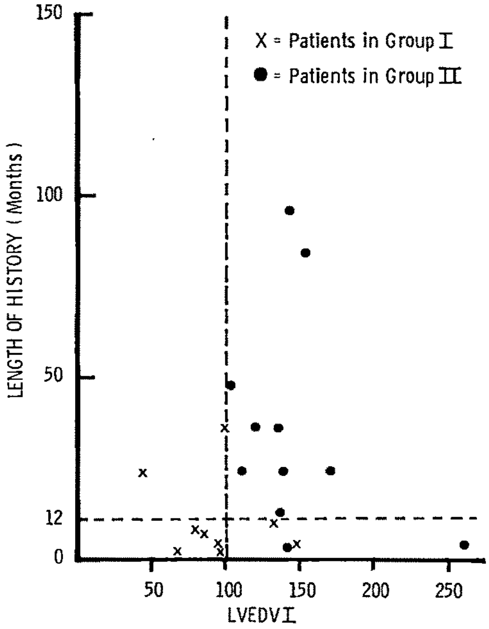

Fig. 3 *Graph showing use of the critical values for length of history and LVEDVI in combination to define a subgroup of patients all of whom respond poorly in the long-term to mitral valve surgery (group 2).*

preoperative (angiographic) ejection fraction ($0{\cdot}65 \pm 0{\cdot}04$) fell significantly ($p < 0{\cdot}01$) after correction of mitral regurgitation to a mean postoperative (echocardiographic) ejection fraction of $0{\cdot}47 \pm 0{\cdot}04$. Similarly, in group 2 the preoperative (angiographic) ejection fraction fell significantly ($p < 0{\cdot}05$) from $0{\cdot}55 \pm 0{\cdot}05$ to $0{\cdot}40 \pm 0{\cdot}04$ postoperatively (Fig. 5). These drops in ejection fraction after operation did not differ significantly ($p > 0{\cdot}5$) between the two groups.

(b) No significant difference between the two groups was found on the basis of preoperative angiographic peak circumferential shortening velocity (V_{CF}), percentage regurgitant volume (% RV), cardiac index, or stroke volume index. Comparison of preoperative (angiographic) peak V_{CF} with postoperative (echocardiographic) mean V_{CF} showed a significant reduction after operation in both groups of patients (Fig. 6). This reduction was equally significant in patients with good and poor surgical results ($p > 1{\cdot}0$ for unpaired Student's t test comparing changes in V_{CF} after surgery in the two groups).

(6) Haemodynamic data

(a) KV max: neither the resting value nor the post-ectopic value differed between the two groups. However, the mean post-ectopic potentiation of KV max was significantly greater ($p < 0{\cdot}05$) in group 1 ($87{\cdot}4 \pm 19{\cdot}8$/s) than in group 2 ($33{\cdot}4 \pm 14{\cdot}0$/s) (Fig. 7).

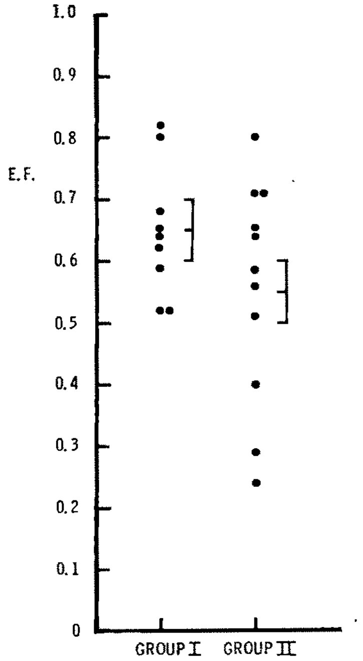

Fig. 4 *Comparison of ejection fraction between patients with a satisfactory (group 1) or unsatisfactory (group 2) response to operation. The group means and SEMs are indicated.*

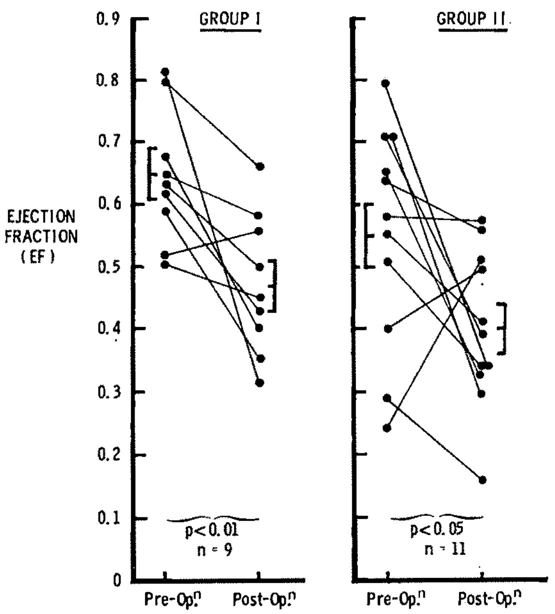

Fig. 5 *Change in ejection fraction after correction of mitral regurgitation in patients responding well (group 1) and poorly (group 2) to operation. Note that the preoperative ejection fractions are angiographic and that those postoperatively are echocardiographic. P values refer to the paired Student's t test. Means and SEMs are indicated.*

(b) dP/dt: neither the pre- nor the post-ectopic value of the max (or min) dP/dt differed significantly between the two groups.

(c) Cardiac index (green dye), stroke volume index, and pulmonary vascular resistance did not differ significantly between the groups.

(7) Type of valve prosthesis

Seven of the 11 patients (64%) who had a Björk-Shiley prosthesis responded well to surgery (group 1) whereas only one out of nine (11%) of those with a Starr-Edwards prosthesis did well postoperatively ($p < 0{\cdot}06$). Those patients receiving a Björk-Shiley prosthesis, however, had a significantly smaller ($p < 0{\cdot}05$) preoperative mean left ventricular end-diastolic volume index ($104{\cdot}6 \pm 10{\cdot}6$ ml/m^2) than those receiving a Starr-Edwards prosthesis ($152{\cdot}4 \pm 20{\cdot}4$ ml/m^2). Other variables of preoperative left ventricular function were no different between the groups (Table 4).

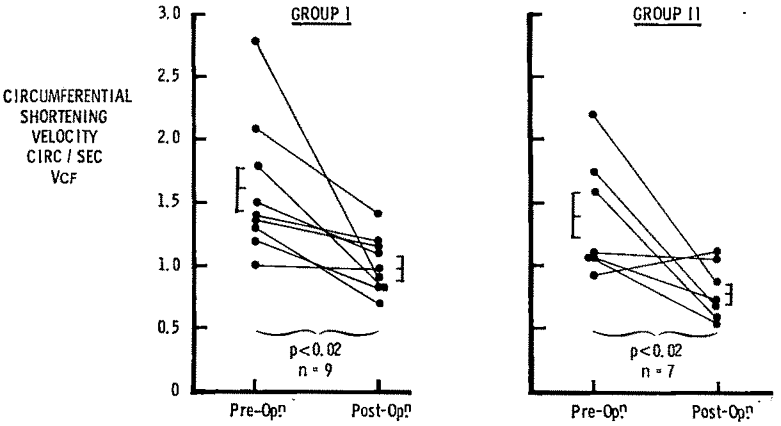

Fig. 6 *Change in V_{CF} after correction of mitral regurgitation in patients responding well (group 1) and poorly (group 2) to operation. Note that the preoperative values are peak $V_{CF}s$ on angiography and the post-operative ones are mean $V_{CF}s$ on echocardiography. P values refer to the paired Student's t test. Means and SEMs are indicated.*

(8) Type of intraoperative myocardial preservation

Seven of the 12 patients (58%) who had intraoperative myocardial preservation by cold potassium cardioplegia had good surgical results (group 1) whereas only two out of 11 (18%) undergoing intermittent aortic cross clamping were in group 1. This difference suggested some beneficial effect from cold potassium cardioplegia but did not reach conventional significance ($p > 0{\cdot}1$). This beneficial effect may be a result of the fact that those patients receiving cold potassium cardioplegia had a significantly smaller ($p < 0{\cdot}01$) mean left ventricular end-diastolic volume index ($103{\cdot}8 \pm 9{\cdot}5$ ml/m^2) than those undergoing intermittent aortic cross clamping ($151{\cdot}3 \pm 17{\cdot}7$ ml/m^2). This suggests that preoperative left ventricular function may have been better in this group than in those undergoing intermittent aortic cross clamping. No difference between the groups was found, however, in other variables of preoperative left ventricular function (Table 4).

(9) Duration of ischaemia

The mean duration of ischaemia in group 1 was $68{\cdot}1 \pm 7{\cdot}0$ min which was in fact longer ($p > 0{\cdot}05$) than that in group 2 ($46{\cdot}1 \pm 4{\cdot}2$ min).

(10) Total bypass time

The mean duration of total bypass was $107{\cdot}1 \pm 8{\cdot}7$ min in group 1 which did not differ signi-

Table 4 *Comparison between patients having Björk-Shiley and Starr-Edwards prostheses on basis of preoperative left ventricular function*

	LVEDVI (ml/m²)	*Post-ectopic potentiation of KV max/s*	*Ejection fraction*	*Peak V_{CF} (circ/s)*
Björk-Shiley	104·6 ±10·6	74·0 ±29·7	0·63 ±0·05	1·6 ±0·2
Starr-Edwards	152·4 ±20·4	32·5 ±8·1	0·51 ±0·05	1·2 ±0·1
t	2·27	1·35	1·76	1·46
p	< 0·05	> 0·2 NS	> 0·05 NS	> 0·1 NS

Values = mean ± standard error of the mean.

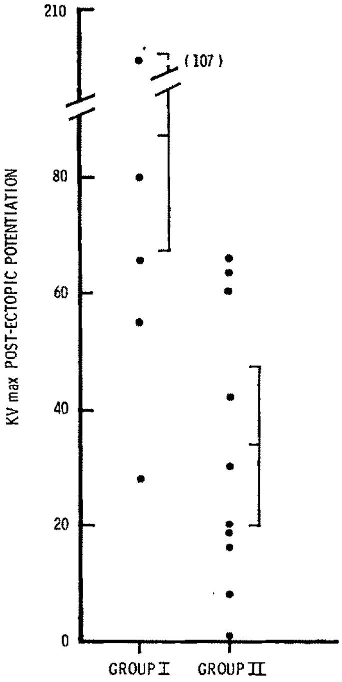

Fig. 7 *Post-ectopic potentiation of KV max according to satisfactory (group 1) or unsatisfactory (group 2) response to operation. The group means and SEMs are indicated.*

ficantly ($p > 0.05$) from that in group 2 (98·8 ±8·8 min).

SECTION B

GLIM analysis of ungrouped data assuming Gaussian distribution again showed a significant effect caused by the length of symptomatic history ($p = 0.022$) when allowance for all other factors was made. The influence of preoperative atrial fibrillation ($p < 0.064$) and of the type of valve prosthesis ($p < 0.084$) was very little short of conventional significance. Other factors analysed in this way showed no significant effects.

SECTION C

Analysis of the grouped data by GLIM allowed simultaneous assessment of any three factors. Length of history, left ventricular end-diastolic volume index, and type of valve prosthesis were the variables included in the model. By exclusion of each in turn, the effect of any one could be gauged allowing for the influence of the other two (but not, of course, for variables not included in the model, for example presence of atrial fibrillation, type of myocardial preservation, etc.). Analysed in this way, length of history ($p < 0.001$), left ventricular end-diastolic volume index ($p < 0.001$), and type of prosthesis ($p < 0.01$) were all significant in determining long-term postoperative function. Thus, it is apparent that the effects of the length of history and of left ventricular end-diastolic volume index become more significant when allowance is made for other factors in the model. Similarly, type of valve (Björk-Shiley versus Starr-Edwards), which was on the borderline of conventional significance on standard χ^2 testing, is shown as being a significant variable when allowance is made for length of history and left ventricular end-diastolic volume index.

Discussion

The haemodynamic consequences of significant mitral regurgitation result from two mechanisms. Firstly, a volume overload (increased preload) is presented to the left ventricle which requires an increase in total left ventricular stroke work and hence increased myocardial oxygen consumption (MVO_2). Secondly, the onset of mitral regurgitation reduces the overall impedance to left ventricular emptying by providing a low impedance outlet (left atrium) in parallel with the systemic circuit. The resulting decrease in afterload permits left ventricular contractile activity to be manifest as enhanced velocity and extent of fibre shortening, rather than as wall tension development.[14] This is closely analogous with isolated muscle experiments which show developed tension to be inversely related to fibre shortening.[15] These changes may be reflected clinically, as enhanced total (angiographic) left ventricular output, ejection fraction, and V_{CF}. Systolic left ventricular pressure also tends to decline more rapidly for an equivalent amount of preload, and, since peak left ventricular and aortic pressures are not significantly altered, integrated left ventricular wall tension (a major determinant of myocardial O_2 consumption) declines more rapidly than normal.[14] The net effect is a stressed left ventricle with increased work load though, initially at least, the increased total stroke volume is expelled relatively efficiently since a greater portion of myocardial oxygen consumption is spent on muscle shortening than on tension development.

A myocardium with good contractile function copes with this stress adequately for a time, but as its inotropic reserve is exhausted compensatory mechanisms become essential to maintain function—principally progressive left ventricular dilatation and eccentric hypertrophy[16]; heterometric autoregulation (Frank-Starling effect); and a decrease in elastic modulus.[17] An enlarging left ventricle would thus signify impaired contractility and an increasing inability to cope with the stress of mitral regurgitation. In the present study, this has been borne out by the significantly larger mean left ventricular end-diastolic volume index preoperatively in those patients who had unsatisfactory long-term results from operation (146·4 ±11·1 ml/m^2) than in those responding well (94·1 ±12·2 ml/m^2). Indeed, 78 per cent in group 1 had a left ventricular end-diastolic volume index $\leqslant 100$ ml/m^2, while 100 per cent in group 2 had an index greater than 100 ml/m^2 implying that this level is critical. An index within the normal range thus indicates a myocardium which is coping well with the increased workload. Values greater than 100 ml/m^2 mean that left ventricular dilatation has occurred to compensate for impaired functional reserve and this is associated with poor long-term surgical results (group 2). The adverse prognostic significance of a large left ventricle found in this study is in close agreement with a recent report that patients with a large rise in pre-mitral valve replacement echocardiographic end-diastolic dimensions undergo progressive deterioration of left ventricular function at long-term follow-up.[18]

The duration of significant mitral regurgitation, as reflected by the length of symptomatic history, was also found to be of prognostic importance. This concurs with the work of Bonchek *et al.*[3] whose prognostic index (a combination of duration of disabling symptoms and response to medical therapy) proved to be the best of 19 preoperative variables at predicting postoperative improvement. In our study, the history was significantly shorter in group 1 (mean 10·2±12·3 months) than in group 2 (mean 47·6±10·4 months). When symptomatic mitral regurgitation was present for one year or more before operation, 79 per cent had a poor outcome, whereas 80 per cent of patients with shorter histories did well. It thus appears that the longer the symptomatic mitral regurgitation is present, the greater is the risk of myocardial impairment and thus of reduced benefit from surgery. One year was found to be the critical time when such changes become apparent indicating that surgery is optimally timed before this.

Simultaneous consideration of left ventricular end-diastolic volume index (>100 ml/m^2) and length of history (>1 year) defined a small subgroup of patients who universally responded badly to operation (Fig. 3). This combined index was more specific than either alone.

The only haemodynamic factor differing significantly ($0·02<p<0·05$) between the two groups was the post-ectopic potentiation of KV max—80 per cent of group 1 showing rises >50/s while 70 per cent of group 2 had values <50/s. The lower values in group 2 might reflect loss of left ventricular function and indicate that the optimum time for surgery had passed. These findings, however, need interpreting with caution since (a) sample sizes were small, (b) one patient in group 1 (case 10) had an extremely large potentiation which would tend to have an inordinate effect on the group mean, and (c) measurements were made during beats of greatly varying RR interval since many patients were in atrial fibrillation at the time of catheterisation. In fact more patients in group 2 (12:86%) were in atrial fibrillation at the time of operation than in group 1 (5:50%) ($p>0·1$). Atrial fibrillation thus seemed to be associated with a worse long-term result from mitral valve replacement—possibly reflecting longstanding mitral regurgitation with left atrial enlargement. Conventional significance was not reached but a definite trend was apparent.

The angiographic ejection fraction is a commonly used index of left ventricular function having some predictive value in valvular heart disease.[19] In the presence of altered loading conditions, however, its usefulness is limited.[20] In mitral regurgitation, the ejection fraction and other ejection phase indices (including peak V_{CF}) may be normal but in many cases are supranormal—thus a value in the normal range may, in fact, reflect impaired contractility. This was underlined in the present study by the fact that both the ejection fraction and V_{CF} fell significantly in both groups 1 and 2 after surgical correction of mitral regurgitation (Fig. 5 and 6). It should be noted, however, that the comparisons are between angiographic (preoperative) and echocardiographic (postoperative) data and in the case of V_{CF} the comparison is between peak (preoperative) and mean (postoperative) values. None the less, these results imply that the presence of significant mitral regurgitation raises the ejection fraction and V_{CF} in ventricles with both good and bad contractile function.

In the present study, many patients with reduced myocardial function had "normal" values for these indices and no mean difference between the groups emerged. Notably, however, no patient in group 1 had an ejection fraction $<0·5$—all three such patients being in the poor outcome group 2. This indicates that in the presence of significant mitral regurgitation, an ejection fraction $<0·5$ is frankly abnormal, appreciable loss of myocardial contractility must have occurred, and a poor long-term surgical result is likely—again in agreement with the echocardiographic findings of Schuler *et al.*[18]

In addition to the variables outlined above which define the preoperative conditions of the left ventricle, several intraoperative variables were found to be independently important in determining surgical outcome. In this small series, those patients who received a Björk-Shiley low profile tilting disc prosthesis did significantly better than those with a Starr-Edwards valve when analysed independently of the effects of left ventricular volume and length of history. It should be noted, however, that the Starr-Edwards group was non-homogeneous, incorporating models 6320 (cloth-covered, composite seat, stellite ball) and 6400 (additional stellite track on the inside of each strut). Advantages claimed for the Björk-Shiley prosthesis include improved haemodynamics because of its low profile and a large orifice-to-tissue-diameter ratio also enabling its use in small hearts. These may be relevant to the present finding of greater improvement in long-term functional ability after its use. Those patients receiving a Björk-Shiley prosthesis had a significantly smaller ($p<0·05$) mean preoperative left ventricular end-diastolic volume index (104·6±10·6 ml/m^2) than those getting a Starr-Edwards valve (152·4±20·4). Though this finding may imply that the Björk-Shiley group had better preoperative left ventricular function, it does not explain the significantly improved results using this valve since the effects of left ventricular end-diastolic volume index were allowed for in the analysis of variance. Also of note is the fact that other indices of left ventricular function (Table 4) not included in the

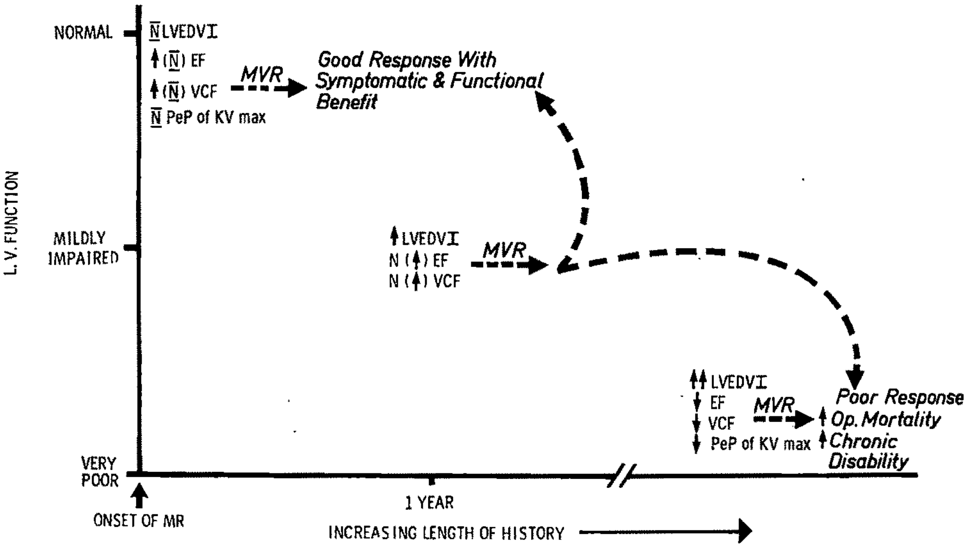

Fig. 8 *Diagrammatic representation of the effect of long-standing significant mitral regurgitation on left ventricular function. The changes in preoperative variables with time are shown and the probable response to mitral valve replacement is indicated.*

analysis of variance model did not differ between those receiving Björk-Shiley and those receiving Starr-Edwards prosthesis.

Those patients receiving cold potassium cardioplegia with St. Thomas' Hospital solution did somewhat better than those undergoing intermittent aortic cross clamping though the difference was not significant on the numbers studied. The former group, however, may have had more impaired preoperative left ventricular function as indicated by a larger mean left ventricular end-diastolic volume index—a finding that might explain their worse results.

Hence, the results of this study support the concepts that in the presence of significant non-rheumatic mitral regurgitation, the contractile state of the left ventricular myocardium at the time of mitral valve operation and the design of the prosthetic valve inserted are the prime determinants of the surgical outcome, and that progressive impairment of contractility is consequent upon longstanding uncorrected disease (Fig. 8). It thus appears that no benefit accrues from withholding surgery once symptoms have appeared or the left ventricle has begun to dilate and that further delay is deleterious, merely allowing progressive left ventricular impairment.

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References

1 Starr A, Edwards ML. Mitral replacement: clinical experience with a ball-valve prosthesis. *Ann Surg* 1961; **154:** 726–40.
2 Starr A, Herr RH, Wood JA. Mitral replacement. *J Thorac Cardiovasc Surg* 1967; **54:** 333–58.
3 Bonchek LI, Anderson RP, Starr A. Mitral valve replacement with cloth-covered composite-seat prostheses. The case for early operation. *J Thorac Cardiovasc Surg* 1974; **67:** 93–109.
4 Bjork VO. Results of mitral valve replacements with the Bjork-Shiley tilting disc valves. In: Kalmanson D, ed. *The mitral valve—a pluridisciplinary approach.* London: Edward Arnold, 1976: 449–55.
5 Kirklin JW, Pacifico AD. Surgery for acquired valvular heart disease. (Second of two parts). *N Engl J Med* 1973; **288:** 194–9.
6 Kirklin JW. Replacement of the mitral valve for mitral incompetence. *Surgery* 1972; **72:** 827–36.
7 Maloney JV Jr, Cooper N, Mulder DG, Buckberg GD. Depressed cardiac performance after mitral valve replacement. *Circulation* 1975; **51** & **52,** suppl I: 1–3, 1–8.
8 Mason SJ, Fortuin NJ. The use of echocardiography for quantitative evaluation of left ventricular function. *Prog Cardiovasc Dis* 1978; **21:** 119–32.
9 Feigenbaum H. *Echocardiography.* 2nd ed. Philadelphia: Lea & Febiger, 1976.
10 Kreulen TH, Bove AA, McDonough MT, Sands MJ, Spann JF. The evaluation of left ventricular function in man: a comparison of methods. *Circulation* 1975; **51:** 677–88.
11 Grossman W, Brooks H, Meister S, Sherman H,

Dexter L. New technique for determinating instantaneous myocardial force-velocity relations in the intact heart. *Circ Res* 1971; **28:** 290–7.

12 Kolettis M, Jenkins BS, Webb-Peploe MM. Assessment of left ventricular function by indices derived from aortic flow velocity. *Br Heart J* 1976; **38:** 18–31.

13 Snedecor GW, Cochran WG. *Statistical methods.* 6th ed. Ames, Iowa: Iowa State University Press, 1967: 258–98.

14 Urschel CW, Covell JW, Sonnenblick EH, Ross J Jr, Braunwald E. Myocardial mechanics in aortic and mitral valvular regurgitation: the concept of instantaneous impedance as a determinant of the performance of the intact heart. *J Clin Invest* 1968; **47:** 867–83.

15 Sonnenblick EH. Implications of muscle mechanics in the heart. *Fed Proc* 1962; **21:** 975–90.

16 Ross J Jr, Sonnenblick EH, Taylor RR, Spotnitz HM, Covell JW. Diastolic geometry and sarcomere lengths in the chronically dilated canine left ventricle. *Circ Res* 1971; **28:** 49–61.

17 Lewis BS, Gotsman MS. Left ventricular function during systole and diastole in mitral incompetence. *Am J Cardiol* 1974; **34:** 635–43.

18 Schuler G, Peterson KL, Johnson A, *et al.* Temporal response of left ventricular performance to mitral valve surgery. *Circulation* 1979; **59:** 1218–31.

19 Cohn PF, Gorlin R, Cohn LH, Collins JJ Jr. Left ventricular ejection fraction as a prognostic guide in surgical treatment of coronary and valvular heart disease. *Am J Cardiol* 1974; **34:** 136–41.

20 Sonnenblick EH, Strobeck JE. Derived indexes of ventricular and myocardial function. *N Engl J Med* 1977; **296:** 978–82.

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Mechanical haemolytic anaemia after valve repair operations for non-rheumatic mitral regurgitation

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SUMMARY Two cases are described in which severe mechanical haemolytic anaemia developed shortly after operation for repair of non-rheumatic mitral regurgitation. One patient had a "floppy" valve and the other cleft mitral leaflets, and both had chordal rupture. In both there was residual regurgitation after repair though in one this was initially only trivial. Clinically manifest haemolysis ceased after replacement of the valve by a frame-mounted xenograft. There are two previously reported cases in which haemolytic anaemia followed an unsuccessful mitral valve repair operation.

Subclinical haemolysis or mild haemolytic anaemia may occur with unoperated valve lesions, but hitherto frank haemolytic anaemia has been observed only when turbulent blood flow is associated with the presence of a prosthetic valve or patch of prosthetic fabric. In these four cases, however, polyester or Teflon sutures were the only foreign material, and it is suggested that when these are used for the repair of leaflets, particularly in non-rheumatic mitral valve disease, they may increase the damaging effect of turbulence on circulating red blood cells.

Mechanical haemolytic anaemia is well recognised as a sequel to open heart operations when there is turbulent blood flow in the presence of prosthetic material. This was first described in a patient who had had an ostium primum atrial septal defect repaired with a Teflon patch,[1] and later in patients with an aortic Starr-Edwards valve and a paraprosthetic leak.[2] It is now known that haemolytic anaemia not uncommonly develops in patients who have had their aortic or, less often, their mitral valve replaced by a mechanical prosthesis without such a fault. Subclinical haemolysis can be detected in many of these patients who are not anaemic. Indeed, it can occur in some patients with aortic valve disease before operation. Two patients have been reported in whom haemolytic anaemia followed mitral valve repair.[3 4] We have recently seen two similar patients, in both of whom the anaemia was corrected by a second operation to replace the repaired valve.

Case reports

CASE 1

A 53-year-old microbiology technician had rheumatic fever at the age of 9. He had been known to have a systolic murmur for at least 25 years. When first seen at the London Chest Hospital in 1966, he had no symptoms of heart disease; he was in sinus rhythm and had a loud mid-late systolic murmur (grade 4/6) with a thrill. The heart was not enlarged on the chest *x*-ray film and pulmonary vascularity was normal. The electrocardiogram showed only sharp T inversion in leads III and aVF. He remained asymptomatic till 1974, though the murmur became pansystolic. During this time the blood pressure averaged 170/100 mmHg. In 1974, he developed atrial fibrillation. Sinus rhythm was restored by direct current countershock but atrial fibrillation recurred two weeks later, despite a small maintenance dose of quinidine (Kinidin durules* 1 bd), and digoxin and practolol were given. After this, his exercise tolerance decreased and there was radiological evidence of increasing heart size and pulmonary venous hypertension.

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* Containing 250 mg quinidine bisulphate.

Cardiac catheterisation and left ventriculography in January 1975 showed pure severe mitral regurgition, with cusp prolapse. The pulmonary artery wedge mean pressure was 24 mmHg, with a 50 mm *v* wave and no mitral end-diastolic gradient.

At operation (Mr J E C Wright), on 19 February 1975, the appearances were those of non-rheumatic mitral regurgitation with ruptured chordae to both anterior and posterior leaflets, which were floppy, redundant, and prolapsing. The posterior cusp was plicated; the prolapsed segment of the anterior cusp was excised as a wedge and the cusp repaired. No prosthetic material was used except for Mersilene (braided polyester) sutures. The postoperative course was uneventful. The haemoglobin level, 15·3 g/dl before operation, fell to 9·0 g/dl three days after operation, and rose to 14·8 g/dl after transfusion. On discharge (6 March) it was 14·6 g/dl. The blood urea before operation was 59 mg/dl (9·8 mmol/l) and on discharge 71 mg/dl (11·8 mmol/l). He remained in atrial fibrillation, but there were no signs of heart failure. There was now a short late systolic murmur only.

On 28 April 1975, he was again defibrillated electrically, and after this took Kinidin durules (2 bd) until 10 June. On that date he reported diarrhoea, attributed to quinidine, and increasing breathlessness. He was pale and jaundiced, but his cardiac condition was unchanged.

Investigations showed: haemoglobin 7·7 g/dl, red blood cells $3{\cdot}1 \times 10^{12}$/l, white blood cells $5{\cdot}3 \times 10^{9}$/l (normal differential), platelets 181×10^{9}/l, reticulocytes 7 to 13 per cent, PCV 24 per cent, MCH 32 pg, MCHC 32·0 g/dl; ESR 140 mm in 1 hour. The blood film showed many fragmented red blood cells. Blood urea was 55 mg/dl (9·2 mmol/l), serum bilirubin (all unconjugated) 1·4 to 1·8 mg/dl (24 to 32 μmol/l), serum hydroxybutyric dehydrogenase 2324 IU/l, serum lactic dehydrogenase 1020 IU/l, serum haptoglobins 0·1 g/l (normal 1·0 to 3·0 g/l), plasma haemoglobin 1·5 g/l. The urine contained urobilinogen and haemosiderin, but no bilirubin or red blood cells. Schumm's test for methaemalbumin was positive. Serum iron and iron-binding capacity, serum vitamin B_{12}, red cell folate, plasma fibrinogen, haemoglobin electrophoresis, and glucose-6-phosphate dehydrogenase were normal. Other investigations giving negative or normal results were osmotic fragility, Ham's acid-serum test, sucrose-haemolysis test, Heinz body preparation, and antinuclear factor. Direct and indirect antiglobulin (Coombs) tests were repeatedly negative.

Bone marrow aspirate showed active normoblastic erythropoiesis with myeloid/erythroid ratio 1:1 and reduced stainable iron. Red cell half-life (^{51}Cr) was 12·0 days (normal 25 to 28 days); there was no significant splenic sequestration and negligible stool loss. Ferrokinetic studies (^{59}Fe) showed rapid clearance and 67 per cent utilisation at six days.

He was treated by blood transfusion, oral iron, and folic acid. During the following 18 months, signs of active haemolysis persisted. The haemoglobin level ranged between 8·8 and 11·0 g/dl and he required transfusion again in October 1976. He remained in sinus rhythm. There were no signs of heart failure, and he still had only a late systolic murmur at the apex. In August 1976, cardiac catheterisation showed normal right heart and left ventricular end-diastolic pressures, and left ventriculography confirmed mild mitral regurgitation, though a minor degree of cusp prolapse was still visible.

During the next year, the clinical signs of mitral regurgitation increased, with a longer and louder apical systolic murmur, and he became increasingly breathless. Concurrently, there was evidence of increasing haemolysis, with a rapid fall in haemoglobin level, and he required repeated transfusions at progressively shorter intervals—an average of 4 to 6 units a month, and during December 1977, 9 units.

At operation on 1 February 1978, the surgeon (Mr J E C Wright) again noted the floppy mitral valve with redundant cusp tissue and dilated valve ring; both leaflets were once more prolapsing allowing moderate central regurgitation. The valve was excised and replaced by a 33 mm frame-mounted xenograft valve (Carpentier-Edwards). After operation, the haemoglobin remained above 12·9 g/dl and no further transfusion was necessary. In the two subsequent years, he has remained well with a haemoglobin level of 13·3 to 14·8 g/dl, and a reticulocyte count repeatedly less than 1 per cent. The blood film is normal, with no fragmented red cells. The red cell half-life (^{51}Cr) is now 23 days. Serum haptoglobins are normal (more than 1·0 g/l), and tests for urinary haemosiderin negative. The xenograft valve remains competent, with no audible murmur, though atrial fibrillation recurred and digoxin has been continued.

CASE 2

A 67-year-old woman was first seen in July 1977 when she gave a one-week history of breathlessness. She was found to be in fast atrial flutter and had signs of severe mitral regurgitation. The chest *x*-ray film showed a slightly enlarged heart and pulmonary venous congestion. She improved with treatment, and sinus rhythm returned. She was anticoagulated with warfarin after an episode of pulmonary infarction and also received frusemide, amiloride, and propranolol.

Cardiac catheterisation and left ventriculography showed pure severe mitral regurgitation with a pulmonary artery pressure of 45/20 mmHg, a 50 mm *v* wave in the pulmonary artery wedge pressure record, and no mitral diastolic gradient. Coronary arteriograms were normal.

At operation (Mr J E C Wright) on 23 January 1978, she was found to have a congenitally abnormal mitral valve with a cleft posterior leaflet and a minor cleft also of the anterior leaflet. There were ruptured chordae to the posteromedial portion of the posterior leaflet which was prolapsing. This was plicated, obliterating the cleft and prolapsing segment. The postoperative course was uneventful. The haemoglobin level was 14·6 g/dl before and did not fall below 12·9 g/dl after operation. An apical systolic murmur was still audible.

In March 1978, she again had signs of severe mitral regurgitation and was in right-sided heart failure. She was found to be severely anaemic.

Investigations showed: haemoglobin 8·8 g/dl, red blood cells $3{\cdot}2 \times 10^{12}$/l, white blood cells $6{\cdot}4 \times 10^9$/l (normal differential), platelets 310×10^9/l, reticulocytes 2·5 to 4·4 per cent, PCV 29 per cent, MCH 28 pg, MCHC 31 g/dl; ESR 10 mm in one hour. The blood film showed fragmented red blood cells. Serum bilirubin was 20 μmol/l, serum hydroxybutyric dehydrogenase 536 IU/l, serum haptoglobins less than 0·5 g/l, and serum iron 6·4 μmol/l. Blood urea, serum vitamin B_{12}, and serum folate were normal. Schumm's test for methaemalbumin was positive. Antinuclear factor was not present and the direct Coombs test was negative. The urine contained urobilinogen and haemosiderin. Red cell half-life (^{51}Cr) was 14·0 days, with no increased uptake in the liver or spleen.

Cardiac catheterisation with left ventriculography was repeated and confirmed that there was still severe mitral regurgitation, with a pulmonary artery pressure 70/30 mmHg and a 30 mm *v* wave in the pulmonary artery wedge pressure record.

At reoperation (Mr J E C Wright) on 24 May 1978, recurrence of mitral regurgitation was found to be the result of further chordal rupture. The valve was excised and replaced by a 31 mm frame-mounted xenograft (Carpentier-Edwards). After operation, the haemoglobin level did not fall below 12·0 g/dl.

In the 20 months since reoperation she has remained in sinus rhythm with competent xenograft valve, though there is a short soft ejection systolic murmur. The haemoglobin level has ranged from 11·8 to 13·9 g/dl; the blood film is normal with no fragmented red cells and reticulocytes never more than 1·8 per cent. Red cell half-life (^{51}Cr) is normal (28 days). There is no methaemalbuminaemia. The urine test for haemosiderin, however, is still weakly positive and serum haptoglobins are less than 0·5 g/l.

Discussion

Both our patients had non-rheumatic mitral valve disease, the first having a "floppy valve" and the second a cleft mitral leaflet, and in both severe mitral regurgitation developed as a result of chordal rupture. In neither was there any associated cardiac lesion. Though evidence of subclinical haemolysis was not sought, neither patient was anaemic before the operation to repair the mitral valve. In neither case was any prosthetic material (except Mersilene sutures) used in the repair procedure, which involved only plication and/or excision of prolapsing segments of the mitral leaflets.

Severe haemolytic anaemia became manifest within two months of operation in case 2 who already had signs of severe recurrent mitral regurgitation resulting from further chordal rupture. In case 1, haemolytic anaemia was recognised four months after the mitral repair procedure at a time when he had clinical signs of only minimal mitral regurgitation, and a year later left ventriculography showed that reflux was still only slight. His condition remained stable until two years after operation, but then clinical signs of increasing mitral regurgitation were accompanied by increasing severity of the haemolytic process.

The haemolytic nature of the anaemia in our cases was established by the high reticulocyte count, increased hydroxybutyric dehydrogenase and lactic dehydrogenase, the presence of urobilinogen and haemosiderin in the urine, and the shortened red cell survival time. Methaemalbuminaemia indicated that haemolysis was intravascular and its mechanical origin was suggested by the presence of fragmented red cells. No other cause of haemolysis was found. In case 1 it was suspected initially that quinidine might be responsible, though he had previously taken quinidine without ill effect. Quinidine may cause haemolysis by forming an immune-complex with drug-specific antibody or in the presence of glucose-6-phosphate dehydrogenase-deficient red cells, but no evidence for either of these mechanisms was found. No other drug taken by either patient could be incriminated.

The final proof that the haemolysis was the result of trauma to red cells and related to the valve lesion was supplied by the response to reoperation with replacement of the regurgitant mitral valve.

In neither case is clinically manifest haemolysis now evident, the haemoglobin level remaining within normal limits with no increase in reticulocyte count. The red cell half-life is normal in case 2 and very slightly reduced in case 1; reduced serum haptoglobin levels and weakly positive tests for urinary haemosiderin are, however, evidence of continuing subclinical haemolysis in case 2.

Anaemia developing after cardiac surgical operations as a result of mechanical haemolysis was first reported by Sayed *et al.*[1] in a patient who had had an ostium primum atrial septal defect closed with a patch of Teflon felt, without repair of the cleft anterior mitral leaflet; overt haemolysis ceased after reoperation when exposed Teflon was covered with endothelium. A further five cases of haemolytic anaemia after repair of ostium primum defects were described by Sigler *et al.*[5] and Verdon *et al.*[6] In all of these the defect had been repaired with a Teflon patch and the cleft mitral leaflet sutured. At reoperation in three of these cases the anterior leaflet of the mitral valve was found to be detached from the Teflon patch used for repair, and in another the patch itself was partially detached; in two[6] the patch was only partially endothelialised. Only two patients survived their second operation[5 6]: one was unimproved and at later necropsy there was still an incompetent mitral valve and exposed Teflon; the other was cured by a successful repair operation.

Haemolytic anaemia was first reported in patients after aortic valve replacement by mechanical prostheses in association with paraprosthetic regurgitation,[2 7 8] but it soon became apparent that this occurred commonly with competent as well as leaking prostheses[9–14] and also, but less often, after mitral valve replacement.[13 15] Stohlman *et al.*[16] had previously found that intravascular haemolysis occurred in dogs after the insertion of a lucite ball valve prosthesis (Hufnagel type) between the left ventricular apex and descending thoracic aorta.

The features common to all these cases are turbulent blood flow resulting from the presence of a mechanical prosthesis and/or paraprosthetic leak or from mitral reflux in ostium primum defects, and the presence of prosthetic material in the circulation. Nevaril *et al.*[17] showed that the morphological changes induced in red cells exposed to shearing stress in vitro were similar to those seen in patients with prosthetic valves and haemolytic anaemia and suggested that a shearing mechanism might be responsible in these cases.

Subclinical haemolysis with shortened red cell survival time, and/or reduced serum haptoglobin levels, and increased serum lactic dehydrogenase or hydroxybutyric dehydrogenase, occurs in many patients with prosthetic valves of all types.[11 18–22] Such patients may not be anaemic, but, because intravascular haemolysis is accompanied by loss of iron as haemosiderin in the urine, a secondary iron-deficiency anaemia may develop[11] even if bone marrow activity is sufficient to compensate for red cell loss.

There have been a few reports of cases of mechanical haemolytic anaemia in association with unoperated valvar disease, usually aortic,[11 23–25] and when large numbers of patients with aortic valve disease have been carefully investigated, evidence of subclinical haemolysis has been found in a small proportion.[10 11 19 25 26] In some patients, reduced haptoglobin levels and fragmented red cells may be the only evidence of haemolysis, and red cell survival times may be normal.[27]

We have found only two previous reports of the development of clinically important haemolytic anaemia in patients with mitral regurgitation, and in both cases this followed a repair operation. Ziperovich and Paley[3] described a patient with rheumatic heart disease who developed mitral regurgitation after a closed mitral valvotomy; massive mitral regurgitation recurred after mitral valve repair (using Tevdek sutures) and severe haemolytic anaemia then developed, with reticulocytosis (13%), jaundice, methaemalbuminaemia, haemoglobinuria, and absent haptoglobins. Clinical haemolysis ceased after replacement of the valve by a Starr-Edwards prosthesis, but serum haptoglobins were still low. Moisey *et al.*[4] observed the development of severe haemolytic anaemia within three weeks of an unsuccessful operation for repair of a cleft mitral anterior leaflet (with polyester sutures) in a 4-year-old child who had previously had a coarctation resected. At reoperation a "loose suture" was observed; after replacement of the valve by a Starr-Edwards prosthesis, haemolytic anaemia did not return, though the red cell half-life was still reduced.

Three of the four cases described (these two and one of our own) still had severe mitral regurgitation after the repair procedure at the time when the haemolytic anaemia became manifest, though our first patient had only trivial mitral regurgitation when he first became anaemic, much less than before operation. Since haemolytic anaemia rarely, if ever, occurs in patients with unoperated mitral regurgitation it is difficult to escape the conclusion that even polyester or Teflon suture material, if critically placed in the path of turbulent blood flow, can increase the damaging effect of turbulence on circulating red cells sufficiently to cause clinically apparent haemolysis. It is possible that the non-rheumatic mitral valve cusp after repair retains sufficient mobility and flexibility to inhibit the growth of "endothelium" over the suture material, though in our cases no observations were made to substantiate this at the time of reoperation. In all four cases replacement of the repaired valve by a prosthesis or zenograft abolished the anaemia, though evidence of subclinical haemolysis was still present in three.

We are grateful to Mr J E C Wright who performed the mitral repair and replacement operations in both cases, and to Professor T A J Prankerd and Dr E C Gordon-Smith for help with the investigation and management of these patients.

References

1 Sayed HM, Dacie JV, Handley DA, Lewis SM, Cleland WP. Haemolytic anaemia of mechanical origin after open heart surgery. *Thorax* 1961; **16:** 356–60.
2 Marsh GW. Intravascular haemolytic anaemia after aortic valve replacement. *Lancet* 1964; **ii:** 986–8.
3 Ziperovich S, Paley HW. Severe mechanical hemolytic anemia due to valvular heart disease without prosthesis. *Ann Intern Med* 1966; **65:** 342–6.
4 Moisey CU, Manohitharajah SM, Tovey LAD, Deverall PB. Hemolytic anemia in a child in association with congenital mitral valve disease. *J Thorac Cardiovasc Surg* 1972; **63:** 765–8.
5 Sigler AT, Forman EN, Zinkham WH, Neill CA. Severe intravascular hemolysis following surgical repair of endocardial cushion defects. *Am J Med* 1963; **35:** 467–80.
6 Verdon TA Jr, Forrester RH, Crosby WH. Hemolytic anemia after open heart repair of ostium primum defects. *N Engl J Med* 1963; **269:** 444–6.
7 Reed WA, Dunn M. Fatal hemolysis following ball valve replacement of the aortic valve. *J Thorac Cardiovasc Surg* 1964; **48:** 436–42.
8 Stevenson TD, Baker HJ. Haemolytic anaemia following insertion of Starr-Edwards valve prosthesis. *Lancet* 1964; **ii:** 982–5.
9 Brodeur MTH, Sutherland DW, Koler RD, Starr A, Kimsey JA, Griswold HE. Red blood cell survival in patients with aortic valvular disease and ball-valve prostheses. *Circulation* 1965; **32:** 570–81.
10 Dupont B, Wennevold A. Mechanical hemolytic anemia in unoperated aortic valve disease. *Acta Med Scand* 1968; **184:** 353–7.
11 Eyster E, Mayer K, McKenzie S. Traumatic hemolysis with iron deficiency anemia in patients with aortic valve lesions. *Ann Intern Med* 1968; **68:** 995–1004.
12 Yacoub MH, Keeling DH. Chronic haemolysis following insertion of ball valve prostheses. *Br Heart J* 1968; **30:** 676–8.
13 Rodgers BM, Sabiston DC Jr. Hemolytic anemia following prosthetic valve replacement. *Circulation* 1969; **39,** suppl I: 155–61.
14 Dave KS, Madan CK, Pakrashi BC, Roberts BE, Ionescu MI. Chronic hemolysis following fascia lata and Starr-Edwards aortic valve replacement. *Circulation* 1972; **46:** 240–9.
15 Marsh GW. Mechanical haemolytic anaemia after mitral valve replacement. *Br Med J* 1966; **ii:** 31–32.
16 Stohlman F Jr, Sarnoff SJ, Case RB, Ness AT. Hemolytic syndrome following the insertion of a lucite ball valve prosthesis into the cardiovascular system. *Circulation* 1956; **13:** 586–91.
17 Nevaril CG, Lynch EC, Alfrey CP Jr, Hellums JD. Erythrocyte damage and destruction induced by shearing stress. *J Lab Clin Med* 1968; **71:** 784–90.
18 Veneziale CM, McGuckin WF, Hermans PE, Mankin HT. Hypohaptoglobinemia and valvular heart disease: association with hemolysis after insertion of valvular prostheses and in cases in which operation had not been performed. *Mayo Clin Proc* 1966; **41:** 657–62.
19 Walsh JR, Starr A, Ritzmann LW. Intravascular hemolysis in patients with prosthetic valves and valvular heart disease. *Circulation* 1969; **39,** suppl I: 135–40.
20 Crexells C, Aerichide N, Bonny Y, Lepage G, Campeau L. Factors influencing hemolysis in valve prosthesis. *Am Heart J* 1972; **84:** 161–70.
21 Nitter-Hauge S, Sommerfelt SC, Hall K-V, Fröysaker T, Efskind L. Chronic intravascular haemolysis after aortic disc valve replacement. Comparative study between Lillehei-Kaster and Björk-Shiley disc valve prostheses. *Br Heart J* 1974; **36:** 781–5.
22 Nitter-Hauge S. Haemolysis after mitral valve replacement with the Björk-Shiley and the Lillehei-Kaster disc valve prosthesis. *Br Heart J* 1976; **38:** 977–80.
23 Massachusetts General Hospital. Case 52: 1964. *N Engl J Med* 1964; **271:** 898–905.
24 Miller DS, Mengel CE, Kremer WB, Gutterman J, Senningen R. Intravascular hemolysis in a patient with valvular heart disease. *Ann Intern Med* 1966; **65:** 210–5.
25 Westring DW. Aortic valve disease and hemolytic anemia. *Ann Intern Med* 1966; **65:** 203–9.
26 Grosse-Brockhoff F, Gehrmann G. Mechanical hemolysis in patients with valvular heart disease and valve prosthesis. *Am Heart J* 1967; **74:** 137–9.
27 Yacoub MH, Rogers K, Crossland-Taylor P. Red cell survival in patients with aortic valve disease. *Thorax* 1965; **20:** 367–9.

Requests for reprints to Dr Michael Honey, London Chest Hospital, Bonner Road, London E2.

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Early systolic closure of the aortic valve

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SUMMARY Six patients with early systolic closure of the aortic valve are described with mitral regurgitation, double outlet right ventricle, left ventricular diverticulum, congestive cardiomyopathy, Eisenmenger ventricular septal defect, and aortic regurgitation with an aneurysmal ascending aorta, respectively. None had evidence of subaortic stenosis.

Early systolic closure of the aortic valve is thus not diagnostic of subvalvular aortic stenosis but is a non-specific finding.

Early or mid-systolic closure of the aortic valve has been described as being of great diagnostic value in the diagnosis of subvalvular aortic stenosis[1–3] whether caused by fixed subaortic stenosis or by hypertrophic obstructive cardiomyopathy. Value has been placed on the presence and even the extent and timing of early systolic closure of the aortic valve in estimating the severity of the outflow tract gradient in subaortic stenosis and the presence of intraventricular gradients in hypertrophic obstructive cardiomyopathy. We present six patients with other heart disorders, with varying degrees of early systolic closure of the aortic valve, none of whom had any evidence of subvalvular aortic stenosis.

Case reports

CASE 1

A 41-year-old woman was entirely asymptomatic until March 1979 when she noted atypical chest pain. Clinically there was no abnormality. Electrocardiogram showed sinus rhythm, normal QRS, and inverted T waves in V3–6, III, and VF. Chest *x*-ray film was normal. Echocardiography (Fig. 1) showed early systolic closure of the aortic valve. At cardiac catheterisation, the left ventricular end-diastolic pressure was normal. There was a left ventricular diverticulum at the apex. There was no cavity obliteration, no gradient was recorded in the left ventricle, and the left ventricular outflow tract was normal haemodynamically and angiographically.

CASE 2

A 73-year-old woman had been noted to have a heart murmur for 12 years and had been breathless on exertion for this period. Five months before admission she began to deteriorate and became orthopnoeic. She was admitted in severe pulmonary oedema with clinical evidence of severe mitral regurgitation. Echocardiography showed intermittent (Fig. 2a and 2b) early systolic closure of the aortic valve and a flail posterior cusp of the mitral valve prolapsing into the left atrium. At operation (Mr M Paneth) the presence of ruptured chordae of the posterior cusp of the mitral valve was confirmed.

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CASE 3

A 12-year-old boy presented with a history of limiting exertional dyspnoea. The abnormal cardiovascular physical findings were confined to ausculta-

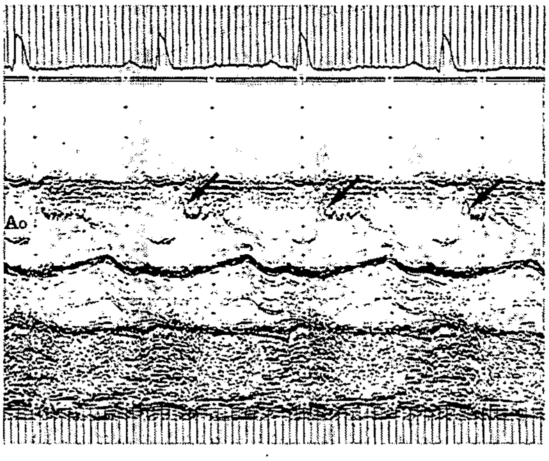

Fig. 1 *Early systolic closure of the aortic valve in a patient with a diverticulum of the left ventricle. Ao, aorta.*

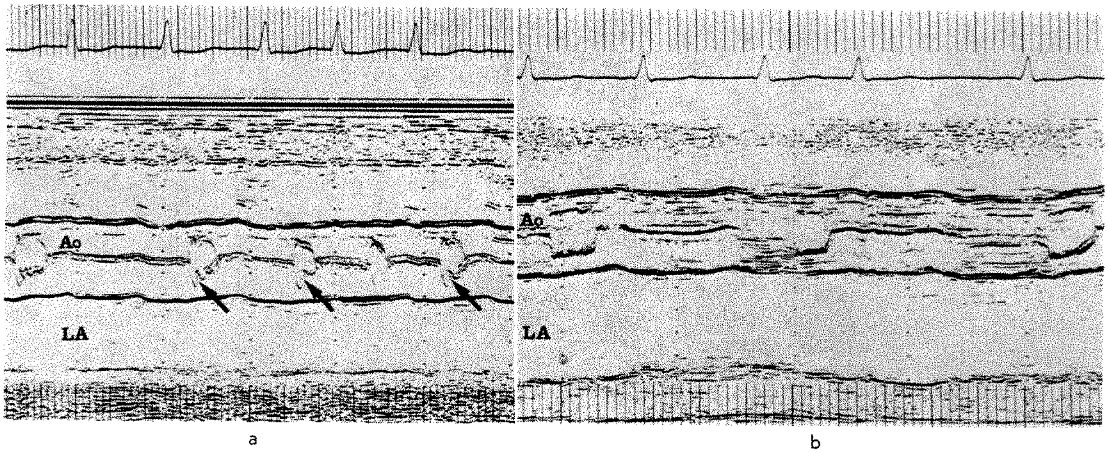

Fig. 2a and b *Intermittent early systolic closure of the aortic valve in a patient with mitral regurgitation due to ruptured chordae. LA, left atrium.*

tion with a normal first sound, single second sound, and a grade 3/6 harsh systolic murmur with a thrill radiating throughout the praecordium and into the carotids. There were no other abnormal physical findings. The electrocardiogram showed sinus rhythm axis + 120 degrees and right ventricular hypertrophy. Chest *x*-ray film was normal.

Echocardiography showed normal left ventricular and mitral valve echoes. A left ventricular to aortic scan showed override of the aorta and the unexpected finding of early systolic closure of the aortic valve (Fig. 3).

A clinical diagnosis of Fallot's tetralogy was made though the possibility of subaortic stenosis was raised by the echocardiogram. At cardiac catheterisation the findings were those of acyanotic Fallot's tetralogy with a tight infundibular stenosis and a ventricular septal defect with equal right and left ventricular pressures. There was no evidence of left ventricular outflow tract obstruction. At operation (Mr C Lincoln) the final diagnosis was revised to double outlet right ventricle with infundibular pulmonary stenosis and an infra-aortic ventricular septal defect. There was no evidence of subaortic stenosis. Postoperative echocardiography showed early systolic aortic valve closure to persist unchanged.

CASE 4

A 76-year-old woman presented with a three-year history of progressively disabling breathlessness. On examination her heart rate was 120/minute in atrial fibrillation, jugular venous pressure raised to 12 cm, BP 140/100 mmHg. The apex was impalpable. The heart sounds were normal with a grade 2/6 pansystolic murmur at the apex. There was no oedema or hepatomegaly and the lung fields were clear. Electrocardiogram confirmed atrial fibrillation with an uncontrolled rate, high left ventricular voltages with non-specific ST-T wave changes laterally. Chest *x*-ray showed an enlarged heart with Kerley B lines and interstitial pulmonary oedema. Echocardiography showed an enlarged left ventricle with diminished posterior wall systolic excursion and an akinetic septum, an enlarged left atrium (5 cm), normal mitral valve echoes, and early systolic closure of the aortic valve (Fig. 4).

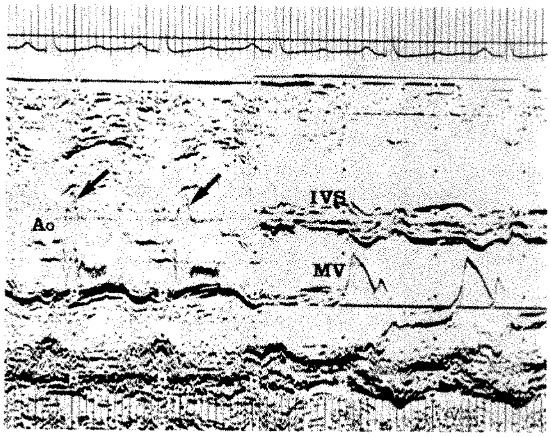

Fig. 3 *M-mode sweep from aorta to mitral valve showing early systolic closure of the aortic valve* (arrowed). *Aortic override of the interventricular septum is also demonstrated. IVS, interventricular septum; MV, mitral valve.*

A diagnosis of congestive cardiomyopathy and atrial fibrillation was made and the patient was treated with digitalis and diuretics. On this treatment she improved, her venous pressure returned to normal, her apical systolic murmur disappeared, and her heart size diminished radiographically. Further investigation was considered inappropriate and she was discharged.

CASE 5

A 44-year-old woman presented with breathlessness on exertion, central cyanosis, and clubbing of fingers and toes. Auscultation disclosed a normal first heart sound, a single second heart sound without murmurs. Blood pressure was 120/70 mmHg. There were no other abnormal findings. She was diagnosed to be suffering from ventricular septal defect with Eisenmenger syndrome and this was confirmed at cardiac catheterisation. Echocardiography showed early systolic closure of the aortic valve (Fig. 5).

CASE 6

A 72-year-old retired accountant presented with a seven months' history of dyspnoea. On examination the pulse was 70/minute, regular, water hammer in character, venous pressure normal. The first heart sound was normal, the second single. There was a grade 3/6 ejection type systolic murmur best heard at the base, radiating into the neck, and a grade 4/6 long early diastolic murmur best heard at the right sternal edge. There was no oedema or hepatomegaly and the lungs were clinically clear. Electrocardiogram showed sinus rhythm and left ventricular hypertrophy "with strain pattern". Chest *x*-ray showed cardiomegaly with unfolding of the aorta and an aneurysm of the ascending aorta. Echocardiography of the aortic valve showed distinct early systolic closure (Fig. 6). Aortography disclosed a greatly dilated ascending aorta, aneurysmal from the aortic valve ring to the origin of the innominate artery accompanied by severe aortic regurgitation. At surgery (Mr M Paneth) the aortic valve consisted of three flimsy leaflets in a dilated ring and there was an aneurysm of the ascending aorta. There was no evidence of subvalvar outflow tract obstruction. After aortic valve replacement and resection of the aneurysm the patient made an uneventful recovery.

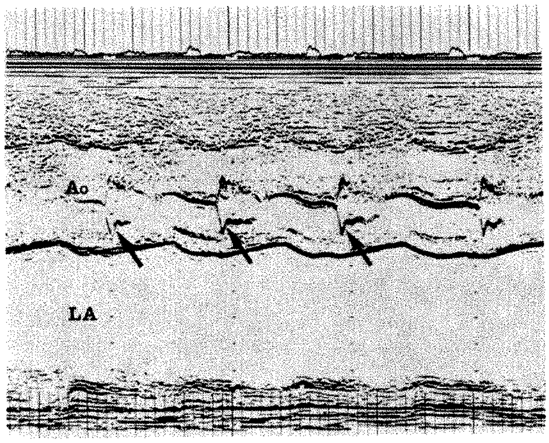

Fig. 4 *Early systolic closure of the aortic valve in a patient with congestive cardiomyopathy.*

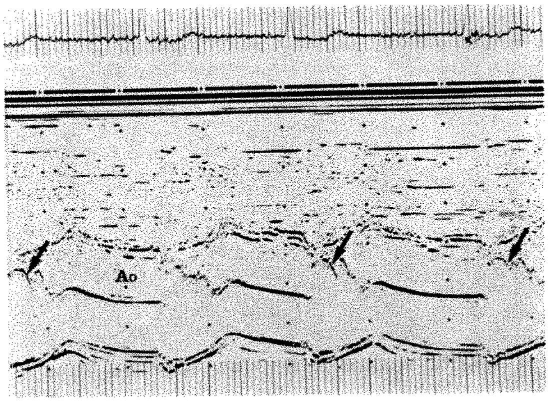

Fig. 5 *Early systolic closure of the aortic valve in a patient with ventricular septal defect complicated by the Eisenmenger reaction.*

Discussion

Early systolic closure of the aortic valve has long been thought to be highly suggestive of either discrete subaortic stenosis or hypertrophic obstructive cardiomyopathy, systolic closure of the aortic valve being said to occur earlier in the former and later in the latter. Davis *et al.*[1] suggested that the echocardiographic findings of "aortic valve closure early in systole, persistent valve closure throughout the remainder of systole, coarse fluttering of the leaflets, and absence of asymmetric septal hypertrophy" are suggestive if not specific for discrete subaortic stenosis, while Silove *et al.*[4] found M-mode echocardiography to be diagnostic in nine out of 10 patients with discrete subaortic stenosis. All nine patients reported by Krajcer *et al.*[2] with discrete subaortic stenosis had early systolic closure, and five out of six retained this feature after operation for relief of left ventricular outflow tract obstruction. Nineteen of 20 patients with discrete subaortic stenosis reported by Kreuger *et al.*[3] had this feature, and they maintained that "the echo features of very early partial closure and valve flutter, and narrow left ventricular outflow tract, are clear enough and specific enough to be used in assessing patients with clinical signs of left ventricular outflow tract obstruction". The occurrence of early systolic closure in hypertrophic subaortic cardiomyopathy is also well recognised. It has been said to correlate well with resting intraventricular pressure gradients, and thought to be a more specific predictor of outflow obstruction than asymmetric septal hypertrophy and systolic anterior movement of the mitral valve.[5 6] However, our cases clearly show that early systolic closure in fact can occur in its various forms in conditions other than subvalvular left ventricular outflow tract obstruction. Cases 1, 3, 5, and 6 were confirmed by cardiac catheterisation and angiography, and cases 2, 3, and 6 at operation. Case 4 had no clinical evidence of either discrete subaortic stenosis or hypertrophic obstructive cardiomyopathy. Early systolic closure of the aortic valve is thus a nonspecific finding in a variety of disorders. Though it can occur in patients with hypertrophic obstructive cardiomyopathy, or discrete subvalvar aortic stenosis, or indeed the tunnel form of subaortic stenosis,[7] it may also be seen in congestive cardiomyopathy, mitral regurgitation, ventricular septal defect,[8] rupture of right sinus of Valsalva aneurysms,[9] diverticulum of the left ventricle, dissection of the aorta,[10] aortic regurgitation with a dilated ascending aorta, and double outlet right ventricle. Its genesis in these conditions can be speculated upon but is unknown.

Although the occurrence of early systolic closure of the aortic valve in the presence of signs of left ventricular outflow tract obstruction may suggest a form of subvalvular stenosis, its diagnostic significance should not be overemphasised.

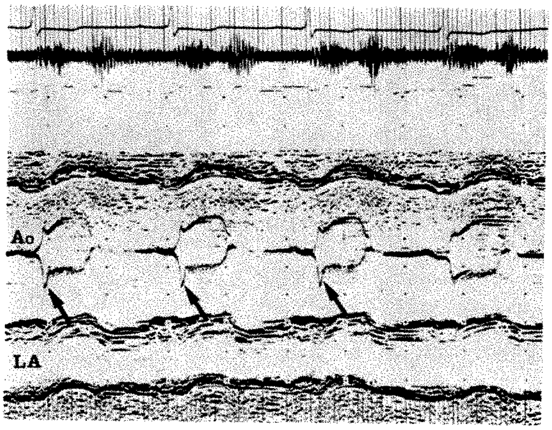

Fig. 6 *Early systolic closure of the aortic valve in a patient with aortic regurgitation and an aneurysmal ascending aorta.*

References

1 Davis RJH, Feigenbaum H, Chang S, Konecke L, Dillon J. Echocardiographic manifestations of discrete subaortic stenosis. *Am J Cardiol* 1974; **33:** 277–80.

2 Krajcer Z, Orzan F, Pechacek LW, Garcia E, Leachman RD. Early systolic closure of the aortic valve in patients with hypertrophic subaortic stenosis and discrete subaortic stenosis. *Am J Cardiol* 1978; **41:** 823–9.

3 Kreuger SK, French JW, Forker AD, Caudill CC, Popp RL. Echocardiography in discrete subaortic stenosis. *Circulation* 1979; **59:** 506–13.

4 Silove ED, Rigby ML, Singh SP. Value of echocardiography in distinguishing valvar from subvalvar aortic stenosis. In: Proceedings of the British Cardiac Society and Swedish Society of Cardiology (abstract). *Br Heart J* 1978; **40:** 443.

5 Feizi Ö, Emanuel R. Echocardiographic spectrum of hypertrophic cardiomyopathy. *Br Heart J* 1975; **37:** 1286–302.

6 Chahine RA, Raizner AE, Nelson J, Winters WL Jr, Miller RR, Luchi RJ. Mid systolic closure of aortic valve in hypertrophic cardiomyopathy. *Am J Cardiol* 1979; **43:** 17–23.

7 Ten Cate FJ, Van Dorp WF, Hugenholtz PG, Roelandt J. Fixed subaortic stenosis. Value of echocardiography for diagnosis and differentiation between various types. *Br Heart J* 1979; **41:** 159–66.

8 Feigenbaum H. *Echocardiography.* 2nd ed. Philadelphia: Lea & Febiger, 1976: 159–61.

9 Johnson ML, Warren SG, Waugh RA, Kisslow JA, Sabiston DC, Lester RG. Echocardiography of the aortic valve in non-rheumatic left ventricular outflow tract lesions. *Radiology* 1974; **112:** 677–84.

10 Candell-Riera J, del Castillo HG, Rius J. Aortic root dissection. Another cause of early systolic closure of the aortic valve. *Br Heart J* 1980; **43:** 579–81.

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Pulmonary wedge injections yielding left-sided echocardiographic contrast*

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SUMMARY Ultrasound contrast on the left side of the heart without the need for left heart catheterisation was achieved by hand injections of 8 to 10 ml 5 per cent dextrose solution through a catheter in the pulmonary wedge position. Injections were performed in 18 patients undergoing routine cardiac catheterisation and M-mode or two-dimensional echocardiography was used. An adequate wedge position was attained in 17 of the 18 patients. Nine had injections through Cournand catheters, three through Swan-Ganz catheters, and five through both. In 11 of these 17 patients left atrial or left ventricular echocardiographic contrast was seen immediately after wedge injection. Two patients showed diminished or absent contrast on later injections from the same position. Better results were obtained with the Cournand catheter (11/15 positive) than with the Swan-Ganz (1/8 positive) catheter. Pulmonary artery injections proximal to the wedge position did not cause left-sided contrast. No complications were observed. The safety of this method remains to be determined.

In the late 1960s, Gramiak and Shah[1] noted that indocyanine green and other solutions caused intracardiac ultrasonic contrast. They speculated that the source of this contrast was microbubbles of air. Since then, further work has more definitely identified the ultrasonic contrast targets to be microbubbles of air introduced during injection.[2 3] Peripheral contrast echocardiology has become an important diagnostic technique.[4–6] Normally, contrast injected peripherally or in the right side of the heart is entirely removed by the lungs, so contrast appearing on the left side of the heart implies an intracardiac right-to-left shunt or an intrapulmonary arteriovenous shunt. In the absence of these anatomical abnormalities, there has been no method of creating left-sided ultrasonic contrast without direct injection, requiring left heart catheterisation.[7]

Several years ago we unsuccessfully attempted to produce contrast in the left side of the heart using Swan-Ganz balloon catheters in the wedge position in six patients (unpublished data). The balloons were inflated during these wedge injections. Recently, Bommer *et al.*[8] from Davis noted that forceful injections in the wedge position in dogs caused ultrasonic contrast on the left side of the heart. We undertook the present study to retest the hypothesis that pulmonary wedge injections may yield left-sided echocardiographic contrast in humans without known pulmonary or intracardiac shunts. Success in attaining left-sided contrast might allow more sensitive diagnosis of left-to-right shunts and better imaging of left-sided cardiac structures by echocardiography, thereby reducing the need in some cases for left heart catheterisation and radiological contrast angiograms.

Patients and methods

Eighteen patients undergoing right and left heart catheterisation for routine clinical indications were studied. There were eight men and 10 women. Their ages ranged from 20 to 67 years (mean 44 years). The diagnoses are listed in the Table.

Number 7 French Cournand or Swan-Ganz catheters were introduced via a right antecubital cutdown and advanced to the wedge position. This was attained without balloon inflation in any of the patients in whom Swan-Ganz catheters were used. Confirmation of wedge position was obtained by

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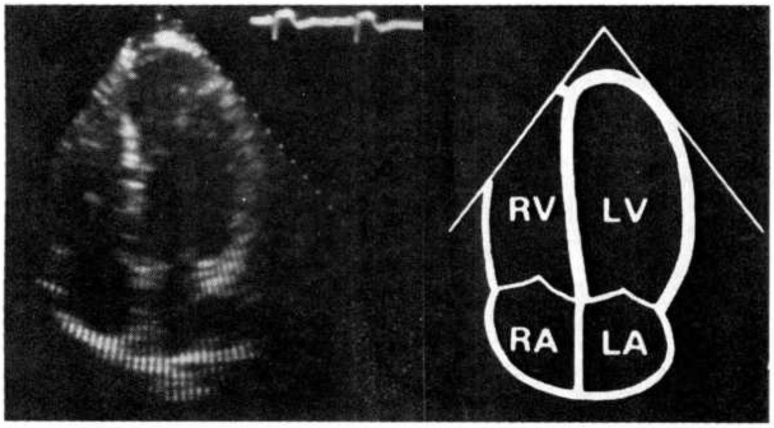

Fig. 1 Left—*stop-frame photograph from the two-dimensional echocardiogram of a subject immediately before wedge injection. Apical four chamber view.* Right—*diagram of left-hand panel. Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.*

fluoroscopy and pressure tracings. Three to seven rapid hand injections of eight to 10 ml 5 per cent dextrose solution were given during normal quiet respiration.

Echocardiographic imaging of the left heart during each injection was performed with the patient in either the supine or slight left lateral decubitus position. An Organon Teknika Echocardiovisor 01 M-mode instrument or a Toshiba SSH-10A phased array two-dimensional ultrasonograph was used.

The symptoms experienced by the patient during injection and subsequent stay in the catheterisation laboratory were carefully monitored, along with electrocardiogram and haemodynamic state. Most of the first 10 patients had post-catheterisation chest films, or lung scans in the anterolateral and left lateral positions between 12 and 36 hours after catheterisation.

Results

An adequate wedge position was attained in 17 of the 18 patients. In the patient in whom the wedge position could not be obtained (Table, case 4), right pulmonary artery injections failed to yield left heart echocardiographic contrast. In 11 of the 17 patients echocardiographic contrast was seen in the left heart immediately after wedge injection. Still frames from a two-dimensional echocardiogram before and immediately after wedge injection in one of these patients are shown in Fig. 1 and 2. Contrast is seen in the left ventricular cavity. Fig. 3 shows an M-mode study at the aorta-left atrial level from another subject, with appearance of contrast in the left atrium after wedge injection.

No patient developed symptoms, deteriorated clinically, or showed any haemodynamic or electrocardiographic changes after the wedge injections.

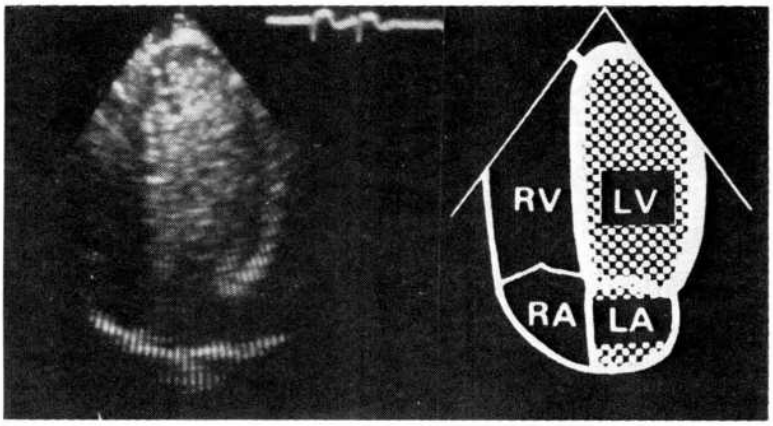

Fig. 2 Left—*stop-frame photograph from the two-dimensional echocardiogram of the subject in Fig. 1, immediately after wedge injection. Apical four chamber view.* Right—*diagram of left-hand panel. Note contrast* (shaded area) *filling the left atrium and left ventricle. Abbreviations as in Fig. 1.*

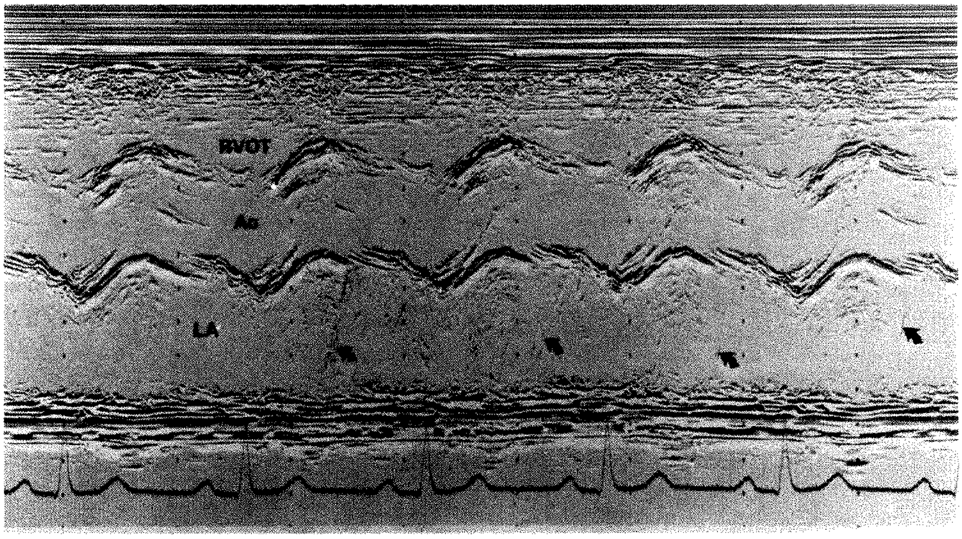

Fig. 3 *M-mode tracing of a subject in the catheterisation laboratory immediately after wedge injection. Note the appearance of fine contrast in the left atrium* (arrows). *Abbreviations: Ao, aorta; LA, left atrium; RVOT, right ventricular outflow tract.*

Chest films were taken between six and 24 hours after catheterisation in five of the first 10 patients studied and were compared with the pre-catheterisation films. None showed new lesions. Lung scans were also negative in the seven patients of the initial first 10 in whom they were performed.

All 17 patients in whom the wedge position was attained had repeated injections. Six persistently showed no left-sided contrast, and two others showed a definite decrease in the amount of left-sided contrast on later compared to earlier injections. In these patients the catheter position was held constant. The other nine patients showed positive findings for three or more injections.

Table *Patient data and outcome of wedge injections*

Case no.	*Age/sex*		*Diagnosis*	*PA pressure systolic/diastolic, mean*	*Mean wedge pressure*	*O₂ saturation (%)*		*Contrast results*	
						Arterial	*Venous*	*Cournand*	*Swan-Ganz*
1	54	M	AS/AR	32/16, 23	13	98	73	−	ND
2	44	M	CAD	×	6	98	×	+	ND
3	37	M	CAD	×	13	96	×	+	ND
4	20	F	ASD	30/16, 19	×	97	MV 62, PA 93	−	ND
5	21	F	Coarct	19/12, 15	7	97	80	−	−
6	48	F	Subvalv AS	21/8, 13	6	96	80	+	ND
7	59	F	CAD	×	×	97	×	+	ND
8	42	M	CAD, MR	19/7, 13	5	98	80	+	ND
9	67	F	AS/AR, MR	32/12, 20	14	95	73	−	ND
10	44	F	CAD	×	15	96	×	+	ND
11	33	F	AR/MR	×	15	×	×	+	ND
12	48	M	CAD	29/15, 21	14	96	75	ND	−
13	51	M	AS/AR	54/22, 34	15	96	70	ND	−
14	50	M	CAD	23/6, 13	7	96	84	ND	−
15	37	F	MS	×	14	×	×	−	−
16	49	F	MS/MR	48/20, 35	31	95	77	−	−
17	31	M	CAD	27/15, 20	15	96	77	+	−
18	58	F	MS/MR	83/33, 54	27	93	67	−, +	+

All pressures are in mmHg.
Abbreviations: AS, aortic stenosis; AR, aortic regurgitation; CAD, coronary artery disease; ASD, atrial septal defect; Subvalv, subvalvular; MR, mitral regurgitation; MS, mitral stenosis; MV, mixed venous; PA, pulmonary artery; ND, injection not done with this catheter. ×, information not obtained or not available; +, left-sided contrast attained; −, no left-sided contrast seen.

Eleven positive studies were obtainable using a Cournand catheter (Table). Injections in an initial position were negative in one patient (case 18) through a Cournand catheter, but became positive after its position was changed. Only one of the eight studies performed with a Swan-Ganz catheter was positive (case 18). Three patients had negative studies with both catheters (cases 5, 15, 16). Except for the patient in whom wedge position could not be obtained (case 4), who had an atropic septal defect, none of the 18 patients had intracardiac shunts. No right-sided contrast was seen after either wedge injections or pulmonary artery injections.

We had the subjective impression that the left-sided contrast was finer than that seen in the right heart after peripheral injections. This finding can be noted in Fig. 3.

Discussion

The results of this study show that in the majority of subjects rapid hand injections in the wedge position cause echocardiographic contrast on the left side of the heart. This could be of help in excluding a left-to-right shunt when performing a right-sided catheterisation as a quick and simple alternative to a saturation run. Its sensitivity needs to be determined, but the high success rate of peripheral venous contrast echocardiography in imaging right-to-left shunts suggests that left-to-right shunts might be very sensitively detected. The high success rate of echocardiographic detection of left-to-right shunting after intracardiac injections leads to the same conclusion.

While it seems likely that the pulmonary capillary "sieve" effect is overcome by rapid wedge injections the exact mechanism by which wedge injections transmit microbubbles through the pulmonary capillary bed is uncertain. Perhaps capillaries are dilated by the force of injection, or, alternatively, the short transit time permits microbubbles which are small enough to pass through pulmonary capillaries and which normally rapidly dissolve because of surface tension effects, to survive long enough to reach the left side of the heart. The "fineness" of the echocardiographic contrast observed in our patients suggests that passage through the pulmonary capillaries alters the microbubble content of the blood but this is a subjective observation and very dependent on individual control settings.

There was no obvious factor apart from the use of the Cournand catheter which strongly correlated with the successful achievement of contrast. Age, sex, diagnosis, pulmonary artery or pulmonary wedge pressure, and arterial and venous oxygen saturations were similar in the groups with successful and unsuccessful studies. Catheter position may be important, for in one patient (case 18) previously negative left-sided contrast was followed by a positive study after catheter repositioning. Injection technique, too, may influence results, especially in regard to the force of injection and the possibility of the inclusion of tiny amounts of air with each bolus.

The technique has not yet been shown to be totally safe, but there are reasons to expect that with care serious complications are unlikely to occur. Firstly, the flushing of catheters in the wedge position in an attempt to improve wedge tracings is a not uncommon occurrence, and, secondly, microbubbles are probably routinely introduced during left-sided injections and flushing during catheterisation, as judged by echocardiography—indeed, echocardiographic contrast was first noted in this way.[1] There is no demonstrable harm attributable to these injections, and it is likely that the smaller microbubbles that pass the pulmonary capillary "sieve" are even less harmful. However, it is important to be aware of the potential hazards from wedge injections: these are (1) lung damage from too forceful an injection (excessive pressure in a pulmonary artery branch from a Swan-Ganz catheter balloon may cause pulmonary artery rupture[9]); (2) prolonged wedging, which may cause pulmonary infarction[10]; and (3) gas embolisation to the coronary, cerebral, or systemic circulations. Thus, a meticulous technique, particularly in excluding obvious air from the wedge injections, as in left-sided intracardiac injections, is mandatory. Until the safety of this technique has been more firmly established, therefore, it must be considered an experimental procedure.

The authors wish to thank Willem Gorissen for technical assistance.

References

1 Gramiak R, Shah PM. Echocardiography of the aortic root. *Invest Radiol* 1968; **3:** 356–66.
2 Barrera JG, Fulkerson PK, Rittgers SE, Nerem RM. The nature of contrast echocardiographic "targets" (abstract). *Circulation* 1978; **57 & 58,** suppl II: 233.
3 Meltzer RS, Tickner EG, Sahines TP, Popp RL. The source of ultrasonic contrast effect. *J Clin Ultrasound* 1980; **8:** 121–7.
4 Kerber RE, Kioschos JM, Lauer RM. Use of an ultrasonic contrast method in the diagnosis of valvular regurgitation and intracardiac shunts. *Am J Cardiol* 1974; **34:** 722–7.
5 Seward JB, Tajik AJ, Spangler JG, Ritter DG.

Echocardiographic contrast studies. Initial experience. *May Clin Proc* 1975; **50:** 163–92.

6 Serruys PW, Hagemeijer F, Roelandt J. Echocardiological contrast studies with dynamically focussed multiscan. *Acta Cardiol* 1979; **34:** 283–90.

7 Serruys PW, van den Brand M, Hugenholtz PG, Roelandt J. Intracardiac right-to-left shunts demonstrated by two-dimensional echocardiography after peripheral vein injection. *Br Heart J* 1979; **42:** 429–37.

8 Bommer WJ, Mason DT, DeMaria AN. Studies in contrast echocardiography: development of new agents with superior reproducibility and transmission through lungs (abstract). *Circulation* 1979; **59** & **60,** suppl II: 17.

9 Golden MS, Pinder T Jr, Anderson WT, Cheitlin MD. Fatal pulmonary hemorrhage complicating use of a flow-directed balloon-tipped catheter in a patient receiving anticoagulant therapy. *Am J Cardiol* 1973; **32:** 865–7.

10 Hagemeijer F, Storm CJ. Fan-shaped shadows due to pulmonary artery catheters: heparin prophylaxis. *Br Med J* 1977; **ii:** 1124.

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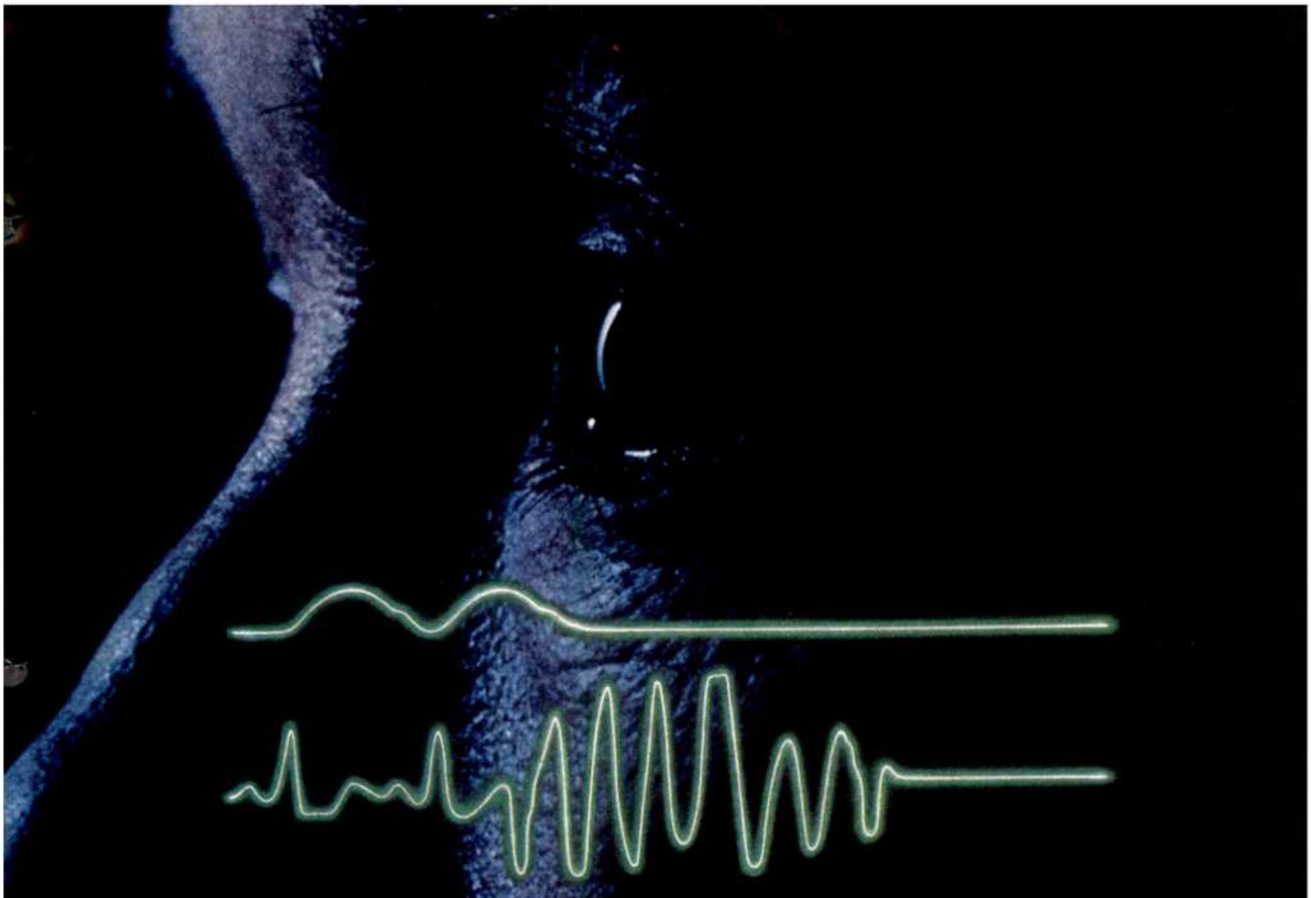

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References 1. Kannel WB, Doyle JT, McNamara PM et al. Precursors of sudden coronary death. *Circulation* 1975; 51(4): 606-613. **2.** Sundquist H, Anttila M, Simon A, Reich JW. Comparative bioavailability and pharmacokinetics of sotalol administered alone and in combination with hydrochlorothiazide. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 565-570. **3.** Jaattela A. The combination of sotalol and hydrochlorothiazide in the treatment of hypertension. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 557-564. **4.** Basson W, Myburgh DP. Synergis of a beta blocker and a diuretic in the once-a-day treatment of essential hypertension. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 571-578. **5.** Reynaert J. Once-a-day treatment with sotalol and hydrochlorothiazide in patients with essential hypertension. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 579-583. **6.** Monatvo H. Sotalol/hydrochlorothiazide in geriatric hypertensive patients. *J Clin Pharmacol* 1979; 19(8/9, pt 2): 584-590. *Trademark. Authorised User. Further information is available to the medical profession on request.

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Echocardiographic differentiation of hypertensive heart disease and hypertrophic cardiomyopathy*

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SUMMARY The clinical differentiation of hypertensive heart disease from hypertrophic cardiomyopathy usually presents no problem but it is less clear whether an echocardiographic distinction can always be made and, if so, what those echocardiographic criteria of difference are. It can be inferred from recent publications that when echocardiographic criteria for hypertrophic cardiomyopathy are met in hypertensive subjects, both diagnoses may be made. This may be unjustified, and in order to clarify this problem the M-mode echocardiographic features of 37 patients with severe systemic hypertension were compared with those of 70 patients with hypertrophic cardiomyopathy and normal blood pressure.

Systolic anterior movement of the mitral valve and/or mid-systolic closure of the aortic valve were found in 82 per cent of patients with obstructive and 35 per cent of patients with non-obstructive hypertrophic cardiomyopathy. These features were not seen in patients with hypertension. The conventional echocardiographic features of left ventricular hypertrophy and function did not permit distinction between hypertensive heart disease and hypertrophic cardiomyopathy.

The echocardiographic diagnosis of hypertensive heart disease from hypertrophic cardiomyopathy is, therefore, difficult unless systolic anterior movement of the mitral valve and/or mid-systolic closure of the aortic valve can be shown.

Echocardiography is a useful procedure in the diagnosis of hypertrophic cardiomyopathy and the presence of asymmetric septal hypertrophy (septal thickness to left ventricular posterior wall ratio ⩾1·3) has, in particular, been considered to be pathognomonic for hypertrophic cardiomyopathy.[1] Subsequently asymmetric septal hypertrophy has been found in many other conditions including hypertension.[2–11] Though earlier reports suggested that the hypertensive heart could be differentiated from hypertrophic cardiomyopathy using echocardiography,[1 12] difficulties have been observed when asymmetric septal hypertrophy (the ratio ⩾1·3) is the diagnostic criterion.[8–11] Moreover, the classical echocardiographic features of hypertrophic cardiomyopathy, including asymmetric septal hypertrophy, have been reanalysed recently and it has been shown that no single M-mode echocardiographic feature is consistently abnormal in hypertrophic cardiomyopathy.[13] We have therefore assessed the M-mode echocardiogram for any features which may differentiate hypertensive heart disease and hypertrophic cardiomyopathy.

Subjects and methods

Thirty-seven patients with severe systemic hypertension were studied by M-mode echocardiography. The echocardiographic features of these patients were compared with those of 70 patients with hypertrophic cardiomyopathy and 37 normal controls.

The patients with systemic hypertension all had a resting diastolic blood pressure of 120 mmHg or more before treatment. All had electrocardiographic evidence of left ventricular hypertrophy with gross ST-T changes. None of these hypertensive patients was in left ventricular failure nor did they have any clinical evidence of left ventricular outflow tract obstruction or coronary artery disease: cardiac catheterisation had not been performed. All patients were on diuretics, beta-adrenergic blocking drugs, methyldopa, minoxidil, or a combination of these

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†Research fellow of the Medical Research Council of Canada.

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drugs. There were 17 men and 20 women, age range 20 to 69, mean 46 years.

The patients with hypertrophic cardiomyopathy were all normotensive and had clinical and angiographic evidence of hypertrophic cardiomyopathy.[14] They were considered to have obstruction if the left ventricular outflow tract gradient at rest or after provocation (with amyl nitrite inhalation or the Valsalva manoeuvre) was equal to or greater than 20 mmHg; 48 patients had resting or provocable obstruction, while 22 patients had no obstruction. There were 42 male and 28 female patients, ranging in age from 12 to 70, mean 44 years.

Thirty-seven normal controls were studied, 14 men and 23 women, age range 20 to 60, mean 34 years.

ECHOCARDIOGRAM

Left ventricular, mitral valve leaflet, aortic root, and left atrial echocardiograms were obtained by standard methods,[15] using an Ekoline 20 ultrasonoscope with a 2·25 MHz transducer, having a repetition frequency of 1000 pulses per second. The output was displayed on a Cambridge strip chart recorder with a simultaneous electrocardiogram. Studies were made with subjects supine or in a partial left lateral position, with the transducer at the left sternal edge.

The following echocardiographic features were assessed (Fig. 1 and 2): (1) ventricular septal thickness at end-diastole, (2) ventricular septal amplitude of motion, (3) ventricular septal thickness to left ventricular posterior wall ratio, (4) left ventricular end-systolic dimension, (5) septal-mitral valve distance at the onset of systole, (6) presence or absence of systolic anterior movement of the mitral valve, and (7) mid-systolic closure of the aortic valve. Features (1) to (4) were assessed from the echocardiograms obtained just below the plane of the mitral valve, where the minor axis of the left ventricle was recorded. Features (5) and (6) were assessed from the echocardiograms obtained at the plane of the mitral valve tips where both anterior and posterior leaflets were recorded simultaneously. Feature (7) was assessed from the echocardiograms obtained at the plane of the aortic root and the left atrium where both anterior and posterior aortic cusps were visualised.

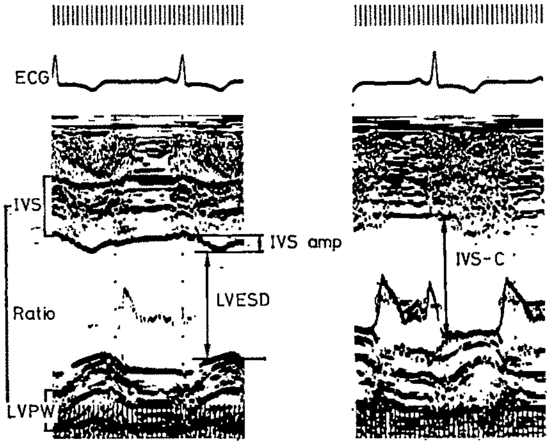

Fig. 1 *The echocardiographic features assessed. IVS, ventricular septal thickness; ratio, septal thickness to left ventricular posterior wall (LVPW) ratio; IVS amp, septal amplitude of motion; LVESD, left ventricular end-systolic dimension; IVS-C, septal-mitral valve distance at the onset of systole; ECG, electrocardiogram.*

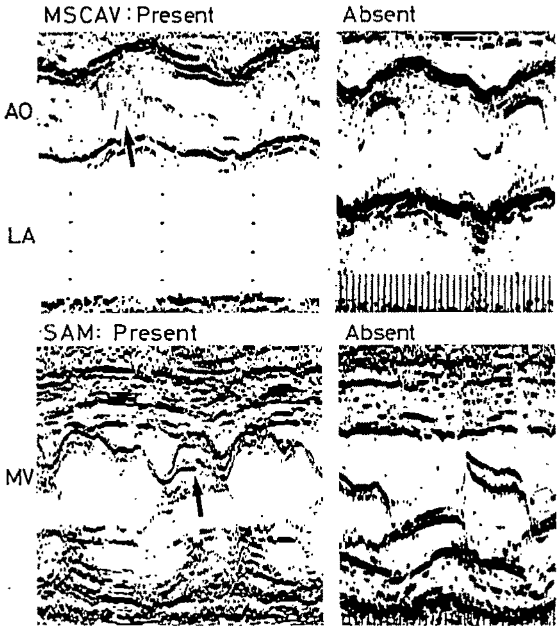

Fig. 2 *The echocardiographic features assessed. MSCAV, mid-systolic closure of the aortic valve; SAM, systolic anterior movement of the mitral valve; AO, aortic root; LA, left atrium; MV, mitral valve.*

STATISTICAL ANALYSIS

Standard statistical analyses were performed. One way analysis of variance was performed initially to test the difference between means of more than two groups; when significant, a two-sample Wilcoxon test was used because the data were not normally distributed.

Results

The results for the seven features analysed are shown in the Table.

HYPERTENSIVE HEART COMPARED WITH NORMAL HEART

The median ventricular septal thickness and ventricular septal thickness to posterior wall ratio in hypertension were significantly greater than in normal controls ($p < 0.001$). The other features were not significantly different, but no normal control or hypertensive patient showed systolic anterior movement of the mitral valve or mid-systolic closure of the aortic valve.

HYPERTENSIVE HEART COMPARED WITH HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

The median ventricular septal thickness and ventricular septal thickness to posterior wall ratio in hypertension were significantly less than in hypertrophic obstructive cardiomyopathy ($p < 0.001$) (Fig. 3). The median ventricular septal amplitude of motion, septal-mitral valve distance at the onset of systole, and left ventricular end-diastolic dimension were all significantly greater in hypertension than in hypertrophic obstructive cardiomyopathy ($p < 0.001$, $p < 0.001$, and $p < 0.05$, respectively). Of 47 patients with hypertrophic obstructive cardiomyopathy, 36 had systolic anterior movement of the mitral valve and 27 of 35 patients had mid-systolic closure of the aortic valve. In 13 patients, the occurrence of mid-systolic closure of the aortic valve could not be adequately assessed.

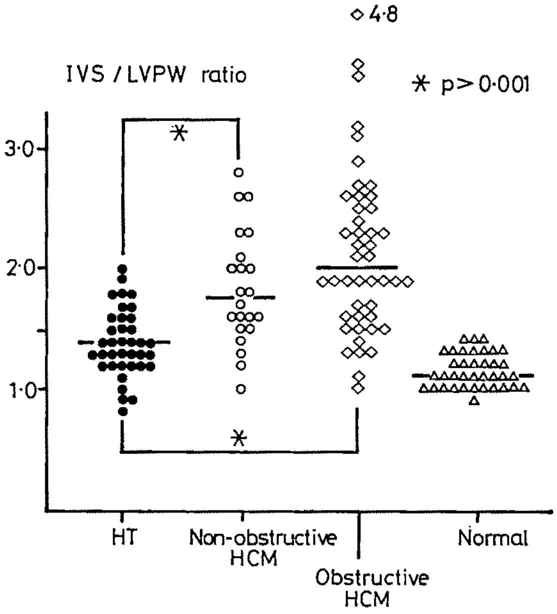

Fig. 3 *Ventricular septal thickness (IVS) to left ventricular posterior wall (LVPW) ratio.*
HT, hypertension; HCM, hypertrophic cardiomyopathy.

Table *Echocardiographic data*

	Normal	*Hypertension*	*Non-obstructive HCM*	*Obstructive HCM*
IVS thickness (mm)	10·0 (9·0–10·0)	14·0 (13·0–16·0)	14·0 (12·0–19·0)	19·0 (17·0–22·0)
IVS amplitude (mm)	7·0 (6·0–8·0)	7·0 (6·0–8·0)	5·0 (4·0–6·0)	4·0 (4·0–5·0)
IVS/LVPW ratio	1·1 (1·1–1·2)	1·4 (1·3–1·5)	1·75 (1·5–2·1)	2·0 (1·8–2·3)
IVS-C (mm)	31·0 (29·0–34·0)	30·0 (28·0–31·0)	24·5 (21·0–29·0)	21·0 (19·0–23·0)
LVESD (mm)	28·0 (27·0–29·0)	25·0 (24·0–30·0)	25·5 (22·0–30·0)	24·0 (21·0–26·0)
SAM	0/37 cases	0/37 cases	6/22 cases	36/47 cases
MSCAV	0/37 cases	0/37 cases	3/14 cases	27/35 cases

HCM, hypertrophic cardiomyopathy; IVS, ventricular septum; LVPW, left ventricular posterior wall; IVS-C, septal-mitral valve distance at the onset of systole; LVESD, left ventricular end-systolic dimension; SAM, systolic anterior movement of the mitral valve; MSCAV, mid-systolic closure of the aortic valve. Figures in parentheses, 95% confidence for the median.

HYPERTENSIVE HEART COMPARED WITH HYPERTROPHIC NON-OBSTRUCTIVE CARDIOMYOPATHY

The median ventricular septal thickness to posterior wall ratio in hypertension was significantly less than in non-obstructive hypertrophic cardiomyopathy ($p < 0.001$) (Fig. 3) and the median ventricular septal amplitude of motion and septal-mitral valve distance at the onset of systole were significantly greater than in non-obstructive hypertrophic cardiomyopathy ($p < 0.001$, and $p < 0.05$, respectively) (Fig. 4 and 5). The median ventricula- thickness and left ventricular end-systolic dimension were not significantly different (Fig. 6 and 7). In non-obstructive hypertrophic cardiomyopathy, six of 22 patients had systolic anterior movement of the mitral valve and three of 14 patients had mid-systolic closure of the aortic valve. In eight patients, mid-systolic closure of the aortic valve could not be adequately assessed.

Discussion

At necropsy left ventricular hypertrophy secondary to hypertension is usually regarded as symmetrical, uniformly involving the septum and the left ventricular posterior wall.[1 12] Echocardiographic work has led to this conventional view being questioned, and asymmetric septal hypertrophy has been observed in hypertension.[8–11] The present study, examining patients with severe systemic hypertension, showed increased septal thickness and increased septal thickness to posterior wall ratio compared with normal controls. This is consistent with the study of Bahler *et al.*[16] which showed that septal thickness has a greater influence on the summated vector and SV1+RV6 than does the thickness of the posterior wall assessed by echocardiography.

Other echocardiographic features of hypertensive patients were similar to those of normal controls. Neither systolic anterior movement of the mitral valve nor mid-systolic closure of the aortic valve were seen either in hypertensive patients or normal controls; this is consistent with the findings of Savage *et al.* in 234 hypertensive patients.[17]

Despite the reports of asymmetric septal hypertrophy in normal children,[2] in athletes,[3 4] and in many other forms of congenital and acquired heart disease,[5–7] including systemic hypertension,[8–11] it is still claimed that asymmetric septal hypertrophy is diagnostic for hypertrophic cardiomyopathy.[18 19] In our study, 70 per cent of hypertensive patients had the ratio ≥1·3, so clearly asymmetric septal hypertrophy is not diagnostic for hypertrophic cardiomyopathy. Other workers have found asymmetric septal hypertrophy in 4 to 47 per cent of hypertensive patients.[8–10 16] All our patients had electrocardiographic evidence of severe left ventricular hypertrophy with pronounced ST-T changes and this may account for the increased incidence of asymmetric septal hypertrophy in comparison with the other studies. Though utilisation of the ratio ≥1·5 improves the diagnostic specificity for hypertrophic cardiomyopathy,[12 20 21] in our study 13 hypertensive patients (35%) had such a ratio.

All the echocardiographic features measured showed significant differences between hypertension and hypertrophic obstructive cardiomyopathy (Table). The majority of patients with hypertrophic obstructive cardiomyopathy showed systolic anterior movement of the mitral valve and/or mid-systolic closure of the aortic valve, and the presence of one of these two features differentiates hypertrophic obstructive cardiomyopathy from hyper-

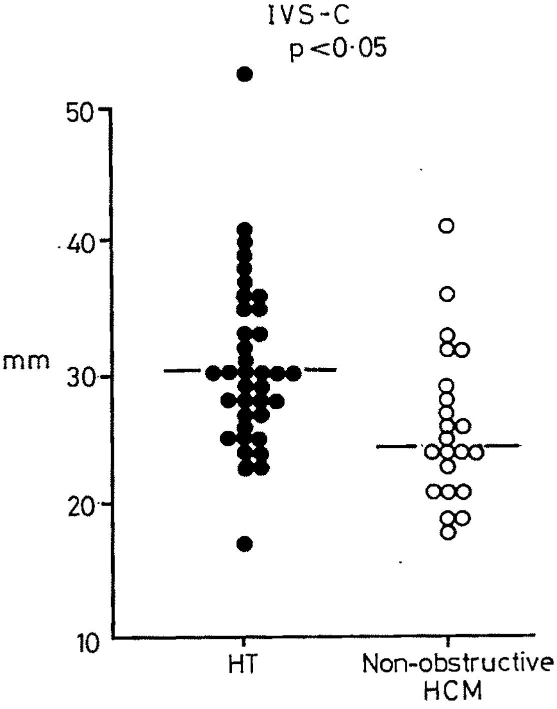

Fig. 5 *Septal-mital valve distance (IVS-C) at the onset of systole. HT, hypertension; HCM, hypertrophic cardiomyopathy.*

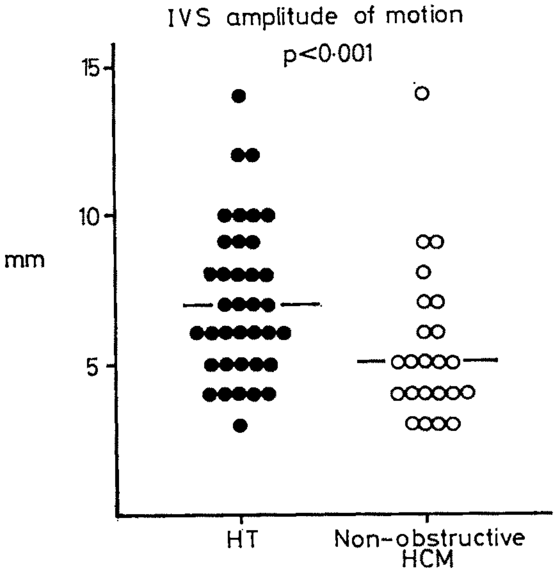

Fig. 4 *Ventricular septal (IVS) amplitude of motion. HT, hypertension; HCM, hypertrophic cardiomyopathy.*

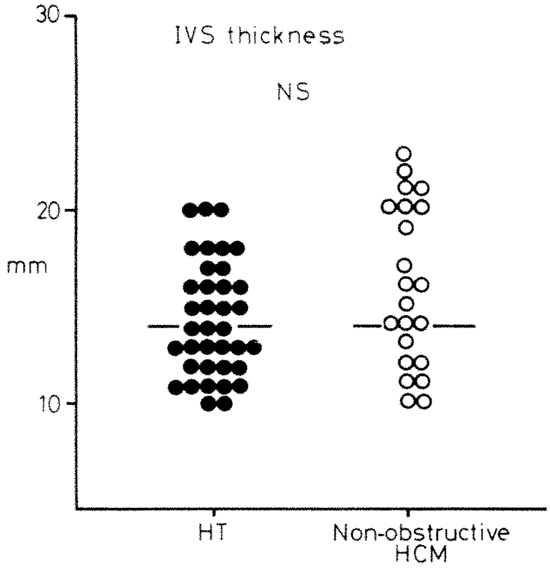

Fig. 6 *Ventricular septal (IVS) thickness.*
HT, hypertension; HCM, hypertrophic cardiomyopathy.

tension. Among nine patients with hypertrophic obstructive cardiomyopathy who did not show either systolic anterior movement of the mitral valve or mid-systolic closure of the aortic valve, six had a ventricular septal thickness to left ventricular posterior wall ratio greater than 2·0; this was not seen in the hypertensive patients (Fig. 3). Only three patients (6%) with hypertrophic obstructive cardiomyopathy, therefore, could not be differentiated from hypertensive patients.

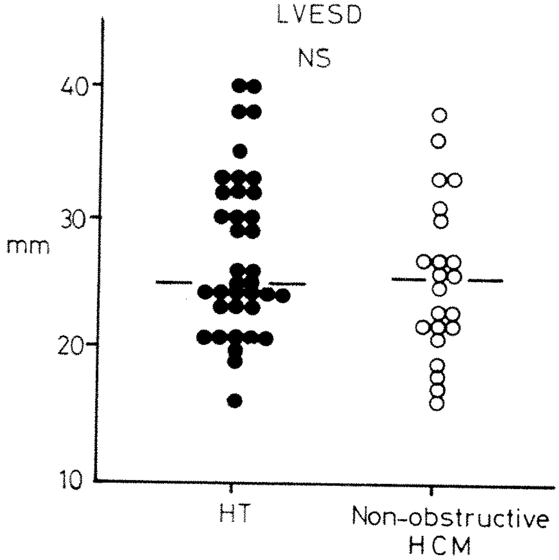

Fig. 7 *Left ventricular end-systolic dimension (LVESD).*
HT, hypertension; HCM, hypertrophic cardiomyopathy.

In the patients with hypertension and those with non-obstructive hypertrophic cardiomyopathy, ventricular septal thickness and left ventricular end-systolic dimension were identical; though septal amplitude of motion, the ventricular septal thickness to left ventricular posterior wall ratio, and septal-mitral valve distance at the onset of systole showed statistical difference between the median values of the two groups, the degree of overlap made differentiation of the individual patient difficult (Fig. 3 to 7). Only a small number of patients with non-obstructive hypertrophic cardiomyopathy had systolic anterior movement of the mitral valve or mid-systolic closure of the aortic valve. The presence of one of these two features or the ratio equal to or greater than 2·0 differentiates only 50 per cent of non-obstructive hypertrophic cardiomyopathy from hypertension. The echocardiographic differentiation of non-obstructive hypertrophic cardiomyopathy from hypertension cannot be made unless the patients with non-obstructive hypertrophic cardiomyopathy have systolic anterior movement of the mitral valve and/or mid-systolic closure of the aortic valve.

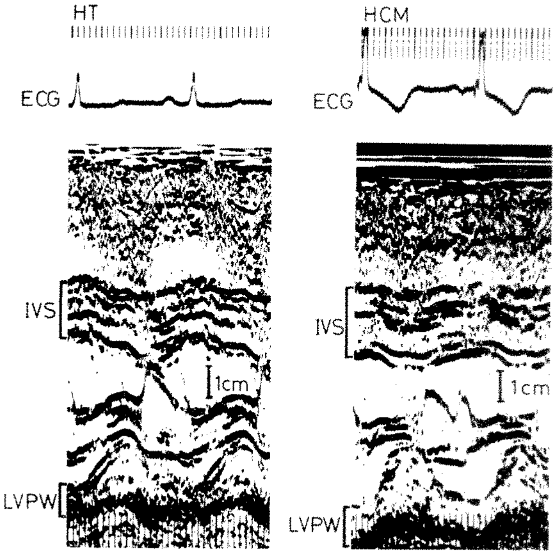

Fig. 8 *Representative echocardiograms of patients with hypertension and hypertrophic cardiomyopathy.*
HT, hypertension; HCM, hypertrophic cardiomyopathy; ECG, electrocardiogram; IVS, ventricular septal thickness; LVPW, left ventricular posterior wall.

Systemic hypertension may coexist with hypertrophic cardiomyopathy. Since the initial description of two patients with hypertension and functional obstruction of the left ventricular outflow tract by Brock,[22] several investigators have reported patients with hypertrophic cardiomyopathy and hypertension.[23–25] In large series, however, hypertension is usually infrequent in patients with hypertrophic cardiomyopathy [26 27] (and McKenna *et al.*, unpublished data on 216 patients). Erroneous use of conservative echocardiographic criteria may cause misdiagnosis of hypertrophic cardiomyopathy in hypertensive patients.

References

1 Henry WL, Clark CE, Epstein SE. Asymmetric septal hypertrophy: echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation* 1973; **47:** 225–33.
2 Larter WE, Allen HD, Sahn DJ, Goldberg SJ. The asymmetrically hypertrophied septum. Further differentiation of its causes. *Circulation* 1976; **53:** 19–27.
3 Roeske WR, O'Rourke RA, Klein A, Leopold G, Karliner JS. Noninvasive evaluation of ventricular hypertrophy in professional athletes. *Circulation* 1976; **53:** 286–92.
4 Menapace FJ, Hammer WJ, Kessler KK, *et al.* Echocardiographic measurements of left ventricular wall thickness in weight lifters: a problem with the definition of ASH (abstract). *Am J Cardiol* 1977; **39:** 276.
5 Maron BJ, Clark CE, Henry WL, *et al.* Prevalence and characteristics of disproportionate ventricular septal thickening in patients with acquired or congenital heart diseases: echocardiographic and morphologic findings. *Circulation* 1977; **55:** 489–96.
6 Feizi Ö, Emanuel R. Echocardiographic spectrum of hypertrophic cardiomyopathy. *Br Heart J* 1975; **37:** 1286–302.
7 Henning H, O'Rourke RA, Crawford MH, Righetti A, Karliner JS. Inferior myocardial infarction as a cause of asymmetric septal hypertrophy. *Am J Cardiol* 1978; **41:** 817–22.
8 Criley JM, Blaufuss AH, Abbasi AS. Nonobstructive IHSS (letter). *Circulation* 1975; **52:** 963.
9 Toshima H, Koga Y, Yoshioka H, Akiyoshi T, Kimura N. Echocardiographic classification of hypertensive heart disease. *Jpn Heart J* 1975; **16:** 377–93.
10 Dunn FG, Chandraratna P, de Carvalho JGR, Basta LL, Frohlich ED. Pathophysiologic assessment of hypertensive heart disease with echocardiography. *Am J Cardiol* 1977; **39:** 789–95.
11 Gibson DG, Traill TA, Hall RJC, Brown DJ. Echocardiographic features of secondary left ventricular hypertrophy. *Br Heart J* 1979; **41:** 54–9.
12 Abbasi AS, MacAlpin RN, Eber LM, Pearce ML. Left ventricular hypertrophy diagnosed by echocardiography. *N Engl J Med* 1973; **289:** 118–21.
13 Doi Y, McKenna WJ, Gehrke J, Oakley CM, Goodwin JF. M-mode echocardiography in hypertrophic cardiomyopathy: diagnostic criteria and prediction of obstruction. *Am J Cardiol* 1980; **45:** 6–14.
14 Cohen J, Effat H, Goodwin JF, Oakley CM, Steiner RE. Hypertrophic obstructive cardiomyopathy. *Br Heart J* 1964; **26:** 16–32.
15 Feigenbaum H. Clinical applications of echocardiography. *Progr Cardiovasc Dis* 1972; **14:** 531–58.
16 Bahler AS, Teichholz LE, Gorlin R, Herman MV. Correlations of electrocardiography and echocardiography in determination of left ventricular wall thickness: study of apparently normal subjects. *Am J Cardiol* 1977; **39:** 189–95.
17 Savage DD, Drayer IM, Henry WL, *et al.* Echocardiographic assessment of cardiac anatomy and function in hypertensive subjects. *Circulation* 1979; **59:** 623–32.
18 Darsee JR, Heymsefield SB, Nutter DO. Hypertrophic cardiomyopathy and human leukocyte antigen linkage: differentiation of two forms of hypertrophic cardiomyopathy. *N Engl J Med* 1979; **300:** 877–82.
19 Savage DD, Seides SF, Maron BJ, Myers DJ, Epstein SE. Prevalance of arrhythmias during 24-hour electrocardiographic monitoring and exercise testing in patients with obstructive and non-obstructive hypertrophic cardiomyopathy. *Circulation* 1979; **59:** 866–75.
20 Shah PM, Sylvester LJ. Echocardiography in the diagnosis of hypertrophic obstructive cardiomyopathy. *Am J Med* 1977; **62:** 830–5.
21 Ten Cate FJ. *Asymmetric septal hypertrophy: echocardiographic manifestations.* Rotterdam: Bronder-Offset BV, 1978: 56–7.
22 Brock RC. Functional obstruction of the left ventricle. *Guy's Hosp Rep* 1957; **106:** 221–38.
23 Moreyra E, Knibbe P, Brest AN. Hypertension and muscular subaortic stenosis. *Chest* 1970; **57:** 87–90.
24 Hamby RI, Roberts GS, Meron JM. Hypertension and hypertrophic subaortic stenosis. *Am J Med* 1971; **51:** 474–81.
25 Alday LE, Wagner HR, Vlad P. Severe systemic hypertension and muscular subaortic stenosis. *Am Heart J* 1972; **83:** 395–400.
26 Braunwald E, Lambrew CT, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic hypertrophic subaortic stenosis. 1. A description of the disease based upon an analysis of 64 patients. *Circulation* 1964; **30,** suppl IV: IV 3–119.
27 Hardarson T, de la Calzada CS, Curiel R, Goodwin JF. Prognosis and mortality of hypertrophic obstructive cardiomyopathy. *Lancet* 1973; **ii:** 1462–7.

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Identification of atrial septal defects by cross-sectional contrast echocardiography

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SUMMARY Cross-sectional echocardiography, combined with injections of contrast into peripheral arm veins, has been used to study 15 patients with atrial septal defects and 10 patients with an intact interatrial septum. Of 11 patients with ostium secundum or sinus venosus atrial septal defects and left-to-right shunts a defect could be visualised in all, and in eight some degree of transfer of contrast from right atrium to left atrium was seen. In three of four patients with a dominant right-to-left shunt a defect was seen and in all there was free transfer of contrast from right atrium to left atrium. Though there may be variable loss of echoes in the septal image in patients with an intact interatrial septum, in general no fixed defect is seen and there is no transfer of contrast from right atrium to left atrium. This is a potentially valuable technique in the assessment of patients in whom an atrial septal defect is suspected.

In the investigation of atrial septal defects by M-mode echocardiography, the features described have included dilatation of the right ventricle, reversed motion of the interventricular septum, and increased amplitude of opening motion of the tricuspid valve relative to the mitral valve.[1-3] These criteria have been found to be lacking in sensitivity and specificity by some workers.[4] In general it is not possible to visualise the interatrial septum directly by M-mode echocardiography though this can be done using cross-sectional echocardiography.[5-9] With the additional use of injections of contrast the presence or absence of interatrial shunts can also be assessed.[9-12] The purpose of this study was to evaluate the use of cross-sectional echocardiography combined with contrast injections into peripheral arm veins in the investigation of patients with atrial septal defects.

Patients and methods

Fifteen patients with atrial septal defects, age range 6 to 53 years, were studied. Eleven patients had a dominant left-to-right shunt shown by estimation of oxygen saturations at cardiac catheterisation, with no detectable right-to-left shunt. Nine of these patients had an ostium secundum atrial septal defect, one a sinus venosus atrial septal defect, and one had Lutembacher's syndrome—an ostium secundum atrial septal defect and mitral stenosis. Four patients who were clinically cyanosed had a dominant right-to-left shunt, two with total anomalous pulmonary venous drainage, one with a secundum atrial septal defect and pulmonary hypertension at systemic level (Eisenmenger syndrome), and one with complex congenital heart disease including dextrocardia and double outlet

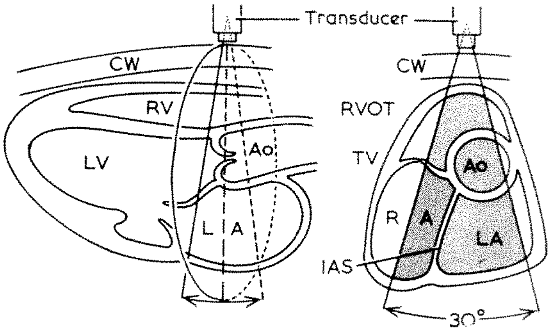

Fig. 1 *Diagram illustrating* (left) *the long axis of the heart and the plane of the ultrasound scan when the short axis view* (right) *is used.*
Ao, aorta; CW, chest wall; IAS, interatrial septum; LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract; TV, tricuspid valve.

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right ventricle with free mixing across an atrial septal defect. All patients except one were also investigated by cardiac catheterisation, the one exception being the patient with Eisenmenger's syndrome in whom the diagnosis was subsequently confirmed at necropsy.

The patients were studied by M-mode and cross-sectional echocardiography using a mechanical 30° sector scanner with a 2·25 MHz transducer (Smith Kline Instrument Company). In all patients a variety of transducer positions were used to visualise the interatrial septum as well as possible.

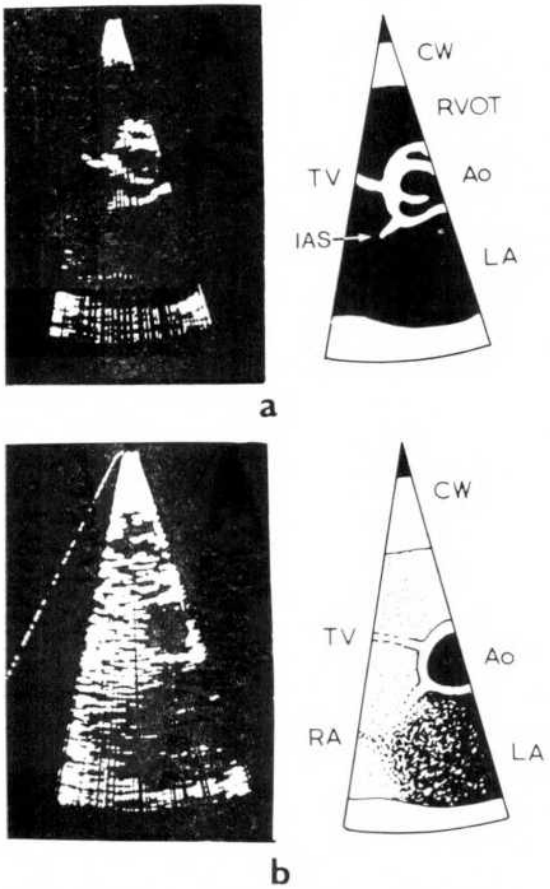

Fig. 2 *Atrial septal defect (ostium secundum) and left-to-right shunt: single frames* (left) *and diagrams* (right); (a) *before, and* (b) *after contrast injections. The interatrial septum (IAS) is shown to be defective of echoes posteriorly, and after injection of contrast into a peripheral arm vein contrast echoes are seen in the left atrium (LA) in addition to filling the right atrium (RA) and the right ventricular outflow tract (RVOT). Ao, aorta; CW, chest wall; TV, tricuspid valve.*

These included apical four-chamber and subxiphoid views in addition to the parasternal short axis view in the plane of the aortic root (Fig. 1), with the transducer held in the third or fourth interspace at the left sternal edge. In some patients better visualisation of the interatrial septal defect was obtained with a modified short axis view, the transducer being held more laterally between the apex and the left sternal edge. Indocyanine green dye, 5 per cent dextrose, or normal saline were injected as contrast into a peripheral arm vein. In addition to the 15 patients with atrial septal defects, 10 patients with an intact interatrial septum were also studied using peripheral contrast injections.

The images were initially viewed on an oscilloscope and stored on magnetic tape. They were subsequently recorded on 35 mm cine film using a cine camera synchronised with the sweep of the scanning ultrasound beam to produce cine film at 15 frames per second.

Results

In all patients the interatrial septum was adequately visualised using the parasternal short axis view or a modified parasternal view with the transducer held more laterally. Good visualisation was achieved in four patients with the apical four-chamber view and in one child, aged 9, with both subxiphoid and apical views. In the 11 patients with an atrial septal defect and a left-to-right shunt a defect was seen in the septal image (Fig. 2 and 3). In three of the patients with a right-to-left shunt a similar appearance was seen (Fig. 4), but in the patient with complex congenital heart disease the septal defect was not consistently seen. The appearance of the interatrial septum in patients with a septal defect differs from that in patients with an intact septum in that, though there is often variable loss of echoes in the image of an intact septum as the septum moves across the plane of ultrasound during the cardiac cycle, there is generally no position of the ultrasound plane in which a fixed defect is seen. In patients with an intact interatrial septum an apparently fixed defect may be seen with certain transducer positions but this appearance is qualitatively different from that seen in most patients with an atrial septal defect in whom the upper edge of the defect is well defined (Fig. 3) and moves with a fixed relation to the aortic root during the cardiac cycle.

After injection of contrast into a peripheral arm vein in patients with an intact interatrial septum, contrast was seen initially in the right atrium and subsequently in the right ventricular outflow tract (Fig. 5). No contrast was seen in the left atrium and the interatrial septum was outlined by the contrast in the right atrium. In the patients with a dominant right-to-left shunt free transfer of contrast from right atrium to left atrium was seen (Fig. 4), with contrast subsequently appearing in the aortic root. In eight of the patients with a dominant left-to-right shunt some degree of transfer of contrast

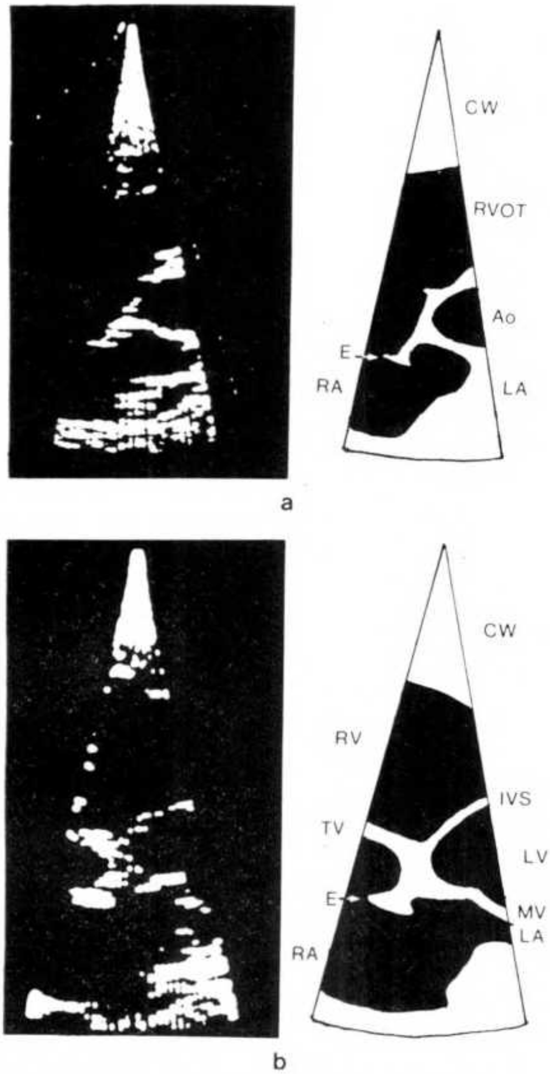

Fig. 3 *Atrial septal defect (ostium secundum) and left-to-right shunt: single frames* (left) *and diagrams* (right); (a) *parasternal short axis view showing a well-defined upper edge (E) to the atrial septal defect, and* (b) *modified parasternal view in the same patient, with the transducer held more laterally between the left sternal edge and the apex. The well-defined edge (E) is clearly seen. The mitral valve (MV) and the upper part of the interventricular septum (IVS) at its junction with the anterior wall of the aortic root are also seen in this view. Ao, aortic root; CW, chest wall; LA, left atrium; LV, left ventricle; RV, right ventricle; RA, right atrium; TV, tricuspid valve.*

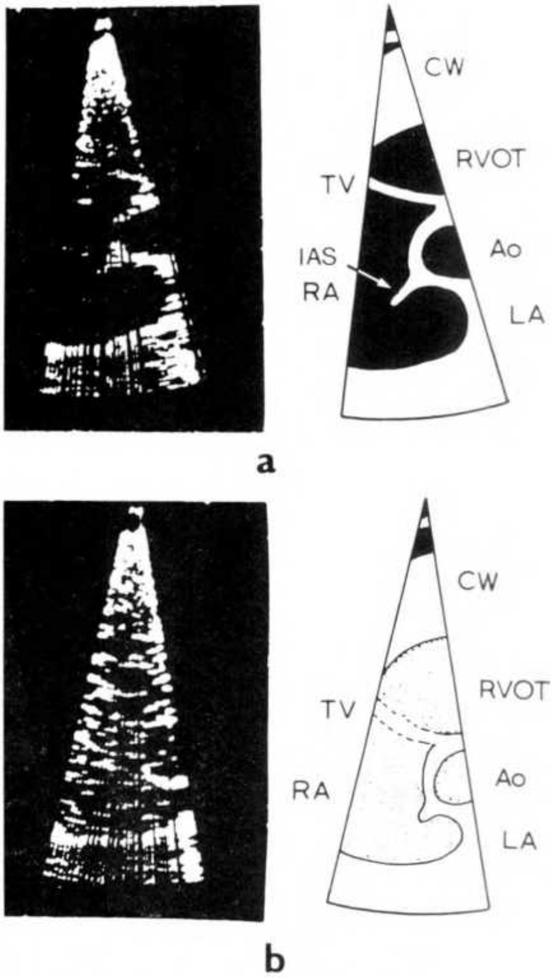

Fig. 4 *Atrial septal defect and right-to-left shunt (total anomalous pulmonary venous drainage): single frames* (left) *and diagrams* (right); (a) *before, and* (b) *after contrast injection. The interatrial septum (IAS) is again defective of echoes posteriorly and free transfer of contrast is observed into the left atrium (LA) with subsequent appearance of the aorta (Ao), with right atrium (RA) and right ventricular outflow tract (RVOT) also filling with contrast echoes. CW, chest wall; TV, tricuspid valve.*

from right atrium to left atrium was seen (Fig. 2). The three patients with a left-to-right shunt in whom contrast was not seen to enter the left atrium were the patient with Lutembacher's syndrome in whom there was a mean pressure difference of 5 mmHg between left atrium and right atrium caused by the presence of mitral stenosis in addition to the secundum atrial septal defect; one patient with a secundum atrial septal defect and a very small left-to-right shunt with a pulmonary to systemic flow ratio of 1·3:1; and a patient in whom the injection of contrast failed to opacify the right atrium adequately.

Attention was paid in all patients to the presence or absence of a negative contrast effect within the right atrium caused by left-to-right shunting of blood across the defect. This could be seen with confidence in only one patient. In this patient the positive transfer of contrast from right atrium to left atrium was particularly obvious.

Discussion

The interatrial septum can be visualised using cross-sectional echocardiography and in patients with an atrial septal defect there is loss of echoes in the posterior part of the septal image. As other workers have found,[5 7–9 12] the appearance of the defect in the septal image can be difficult to distinguish from the variable loss of echoes that is seen in patients with an intact interatrial septum. We have found that in most patients with an atrial septal defect the appearance of the edge of the anterior part of the septal image differs qualitatively from that seen in normal patients in that the echoes from the edge are more intense and that this edge moves with a constant relation to the aortic root during the cardiac cycle. Though the appearance of an edge can be produced in patients with an intact interatrial septum, the position of this edge tends to vary more in relation to the aortic root during the cardiac cycle and with different planes of ultrasound.

The short axis view in the plane of the aortic root, modified in some cases by holding the transducer more laterally between the left sternal edge and the apex, was found to be the most satisfactory view for visualisation of the interatrial septum in this group of patients. Other workers have found apical or subxiphoid views more useful for the identification of atrial septal defects.[6 7] This difference may be partly explained by the age of our patients, all but two of whom were adults, since it is often not possible in adults to obtain these views adequately.

We did not include patients with ostium primum atrial septal defects in this study since the appearance of the interatrial septum and atrioventricular valves differs from the normal appearance in a number of important respects[5] which make this group of patients more readily distinguishable from patients with ostium secundum or sinus

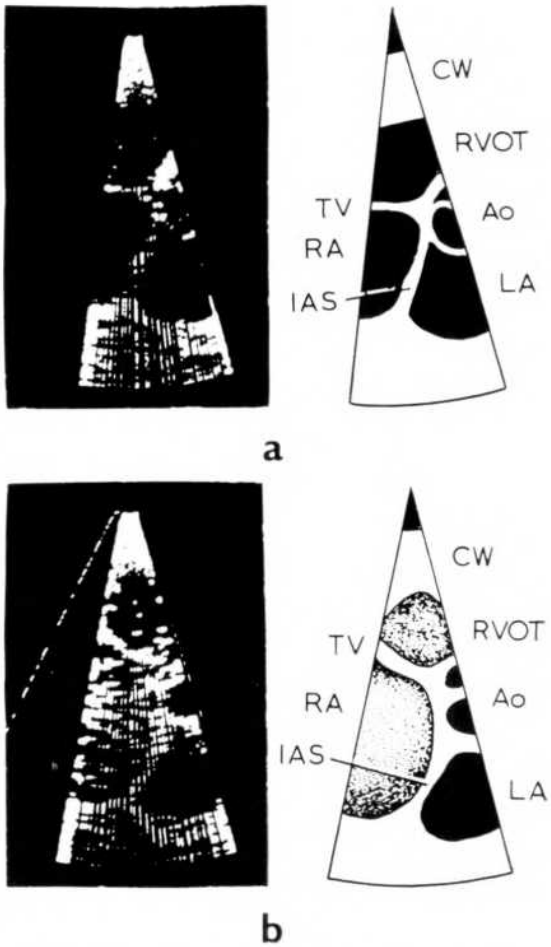

Fig. 5 *Intact interatrial septum: single frames* (left) *and diagrams* (right); (a) *before, and* (b) *after contrast injections. The intact interatrial septum (IAS) separates the right atrium (RA) from the left atrium (LA), and after injection of contrast into a peripheral arm vein contrast echoes fill the RA and right ventricular outflow tract (RVOT), outlining the IAS. In this patient the RA and RVOT are enlarged because of a large left-to-right shunt resulting from a communication between the LA and coronary sinus, with a persistent left superior vena cava. Ao, aorta; CW, chest wall; TV, tricuspid valve.*

venosus defects and patients with intact interatrial septa.

In an individual patient examined by an experienced operator the appearance of the septal image can strongly suggest the presence of an ostium secundum atrial septal defect. This however is essentially a negative and, to some extent, a subjective finding. The transfer of contrast echoes from right atrium to left atrium is a positive feature which confirms the presence of a defect. The results we have obtained using this technique are similar to those of other workers[9–11] in that most patients with an atrial septal defect and a left-to-right shunt show some degree of transfer of contrast echoes from right atrium to left atrium after injection into a peripheral arm vein.

We have not been able to confirm the findings of Weyman *et al.*[12] who found that the appearance of a negative contrast effect to the right of the interatrial septum was a more useful indicator of a left-to-right shunt than either the appearance of the defect itself or the positive transfer of contrast echoes from right atrium to left atrium. This negative contrast effect is more difficult to assess objectively than the appearance of contrast echoes in the unopacified left atrium, and on theoretical grounds it may be difficult to distinguish from other negative contrast effects caused by blood entering the right atrium from the coronary sinus and venae cavae.

The technique of cross-sectional echocardiography combined with contrast injections may also be useful when no fixed defect can be seen in the septal image and no transfer of contrast from right to left atrium is seen, since these negative findings indicate that the interatrial septum is intact. In one of the patients studied an atrial septal defect was strongly suspected on clinical grounds. The patient was subsequently found at cardiac catheterisation to have a persistant left superior vena cava with left atrial and coronary sinus communications, and cross-sectional contrast echocardiography helped to confirm that the interatrial septum was intact (Fig. 5), in addition to demonstrating the enlarged coronary sinus and left atrial communication.[13]

Conclusions

Cross-sectional echocardiography is a valuable technique in the assessment of patients in whom an atrial septal defect is suspected. A relatively specific appearance of the interatrial septum is observed in patients with atrial septal defects and injection of contrast into a peripheral arm vein helps to confirm the presence or absence of a defect.

References

1 Diamond MA, Dillon JC, Haine CL, Chang S, Feigenbaum H. Echocardiographic features of atrial septal defect. *Circulation* 1971; **43:** 129–35.

2 McCann WD, Harbold NB Jr, Giuliani ER. The echocardiogram in right ventricular overload. *JAMA* 1972; **221:** 1243–5.

3 Radtke WE, Tajik AJ, Gau GT, Schattenberg TT, Giuliani ER, Tancredi RD. Atrial septal defect: echocardiographic observations. Studies in 120 patients. *Ann Intern Med* 1976; **84:** 246–53.

4 Hagan AD, Francis GS, Sahn DJ, Karliner JS, Friedman WF, O'Rourke RA. Ultrasound evaluation of systolic anterior septal motion in patients with and without right ventricular volume overload. *Circulation* 1974; **50:** 248–54.

5 Dillon JC, Weyman AE, Feigenbaum H, Eggleton RC, Johnston K. Cross-sectional echocardiographic examination of the interatrial septum. *Circulation* 1977; **55:** 115–20.

6 Bierman FZ, Williams RG. Subxiphoid two dimensional imaging of the atrial septum (abstract). *Am J Cardiol* 1978; **41:** 354.

7 Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: technique, image orientation, structure identification and validation. *Mayo Clin Proc* 1978; **53:** 271–303.

8 Schapira JN, Martin RP, Fowles RE, Popp RL. Single and two-dimensional echocardiographic features of the interatrial septum in normal subjects and patients with an atrial septal defect. *Am J Cardiol* 1979; **43:** 816–9.

9 Fraker TD Jr, Harris PJ, Behar VS, Kisslo JA. Detection and exclusion of interatrial shunts by two-dimensional echocardiography and peripheral venous injection. *Circulation* 1979; **59:** 379–84.

10 DeMaria AN, Bommer W, George L, Neumann A, Weinert L, Mason DT. Combined peripheral venous injection and cross-sectional echocardiography in the evaluation of cardiac disease (abstract). *Am J Cardiol* 1978; **41:** 370.

11 Kronik G, Slany J, Moesslacher H. Contrast M-mode echocardiography in diagnosis of atrial septal defect in acyanotic patients. *Circulation* 1979; **59:** 372–8.

12 Weyman AE, Wann LS, Caldwell RL, Hurwitz RA, Dillon JC, Feigenbaum H. Negative contrast echocardiography: a new method for detecting left-to-right shunts. *Circulation* 1979; **59:** 498–505.

13 Foale RA, Bourdillon PDV, Somerville J, Rickards AF. Echocardiographic features of anomalous systemic and coronary venous return (abstract). *Br Heart J* 1979; **41:** 381–2.

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Br Heart J 1980; **44:** 406–10

Prediction of left ventricular pressure in infants with aortic stenosis*

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SUMMARY Peak systolic left ventricular pressure was predicted in five infants with aortic stenosis by use of a wall stress constant, K. K was determined in 10 normal infants according to the formula $K = P \cdot Ds/Ws$, where P = arterial pressure by Doppler, Ds = end-systolic LV dimension, and Ws = end-systolic wall thickness. Left ventricular peak systolic pressure was estimated in five infants using the formula $P = K \cdot Ws/Ds$. Excellent correlation was obtained between measured left ventricular pressure and left ventricular-aortic pressure difference at cardiac catheterisation and echo estimates. Echocardiographic assessment of the severity of aortic stenosis may be applied to infants with good results.

Determination of the severity of left ventricular outflow tract obstruction by single crystal echocardiography was first reported by Bennett *et al.* in adult patients with valvular aortic stenosis.[1] The peak systolic left ventricular pressure and peak systolic pressure difference across the valve were predicted using relative wall thickness times a constant as an index of left ventricular systolic wall stress. The validity of this wall stress index was based on the observation that, given normal left ventricular function, the magnitude of concentric ventricular hypertrophy increases in response to increased afterload until wall stress is normalised.

The reproducibility and reliability of the wall stress index were subsequently confirmed in children by several investigators.[2–5] To date, however, these measurements have not been applied to infants under 1 year of age with valvular aortic stenosis. This report communicates our experience with the wall stress index in this age group.

Subjects and methods

Data were obtained from 15 subjects less than 1 year of age. Informed consent was obtained from the parents/guardians of each infant. Group 1 (control subjects) consisted of 10 infants aged 1 to 11 months, without evidence of cardiopulmonary disease, who underwent echocardiographic examination during well-baby visits or while in hospital for minor surgical procedures. The constant, K, was derived from this group.

Group 2 (aortic stenosis patients) consisted of five infants, aged 2 weeks to 11 months, with valvular aortic stenosis confirmed by complete right and left heart catheterisation. All infants in group 2 had prominent left ventricular forces for age on scalar electrocardiogram. Two infants (cases 2 and 3) were in congestive heart failure as manifested by tachypnoea and poor feeding.

Cardiac catheterisation was performed without premedication. Simultaneous left ventricular and descending aortic pressure was measured in four infants and Doppler left brachial pressure in the fifth. The peak left ventricular pressure ranged from 100 to 210 mmHg, and the peak pressure difference across the valve ranged from 10 to 110 mmHg. The two infants in congestive heart failure were shown to have left-to-right atrial level shunts, left atrial, and pulmonary artery hypertension (mean left atrial pressure 12 and 13 mmHg; mean pulmonary artery pressure 55 and 25 mmHg, respectively). There were no associated cardiac defects. Three patients required surgical intervention, with two survivors.

Echocardiographic assessments were performed with a Smith-Kline Ekoline 20 ultrasonoscope and a Smith-Kline strip chart recorder using light-sensitive paper. A 5 MHz non-focused transducer was used. The examination was carried out, with the infant supine, and with the transducer in the

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third or fourth intercostal space along the left sternal border, and angled inferiorly and laterally until the posterior mitral valve apparatus was located. A technically adequate study required sweeping the left ventricle from the aorta to the apex, thus allowing visualisation and measurement of the left ventricular dimensions at the free edge of the mitral leaflet.

Measurements of end-diastolic wall thickness (Wd), end-systolic wall thickness (Ws), end-diastolic cavity dimensions (Dd), and end-systolic cavity dimensions (Ds), were made from the echocardiographic trace (Fig. 1). Wall thickness was measured from the endocardium to the epicardium at end-diastole, corresponding to the Q wave of the simultaneous electrocardiogram; and at end-systole, the point of maximal anterior motion of the left ventricular posterior wall. Transverse left ventricular end-diastolic and end-systolic cavity dimensions were measured from the endocardial septal echo to the endocardial free wall echo at the Q wave of the electrocardiogram, and at the maximal anterior free wall excursion, respectively.

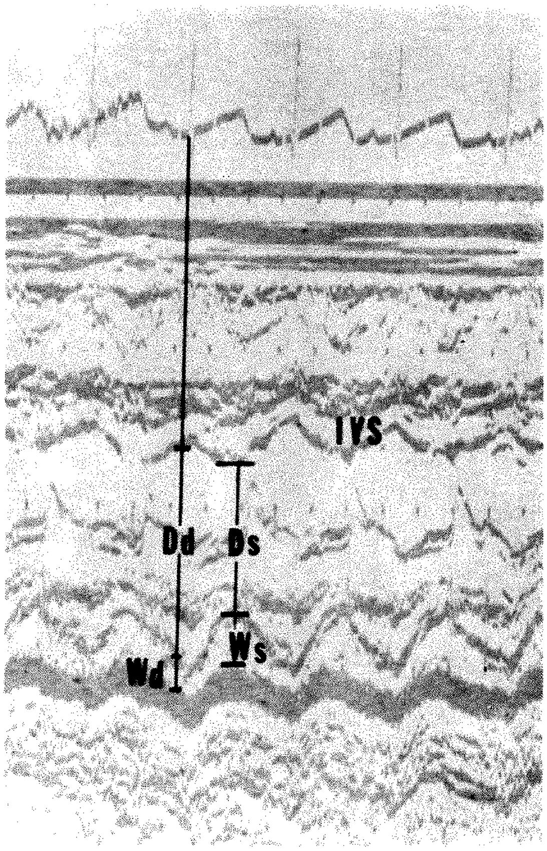

Fig. 1 *Representative echocardiogram from a normal infant showing the location of the sites for measurement of left ventricular cavity diastolic dimension (Dd), systolic dimension (Ds), end-diastolic wall thickness (Wd), and end-systolic wall thickness (Ws). IVS, intraventricular septum.*

Peak systolic blood pressure was measured at the time of the echocardiographic examination in each infant, using a Doppler system. The method of Bennett *et al.* was then used to derive a pressure constant (K) from the subjects in group 1: $K = P \, . \, Ds/Ws$, where peak systolic blood pressure was assumed to equal left ventricular pressure in normal controls.

The constant derived from group 1 (K in mmHg) was then used to estimate peak left ventricular pressure in the patients with aortic stenosis, where $P = K \, . \, Ws/Ds$. The peak systolic pressure difference was determined by subtracting the Doppler systolic pressure from predicted left ventricular peak systolic pressure by echo. In group 2, the results were compared with those found at catheterisation.

Results

The echocardiographic measurements for group 1 are shown in Table 1. End-diastolic wall thickness, end-systolic wall thickness, end-diastolic cavity dimensions, and end-systolic cavity dimensions were all within normal limits. Relative wall thickness (Ws/Ds) ranged from 0·29 to 0·52 (mean ± a standard deviation of 0·4 ± 0·07). The percentage of wall thickening with systole ranged from 48 to 114 per cent (mean 72·5 ± 19·0%). Shortening fraction ranged from 27 to 42 per cent (mean 34 ± 4·9%). Peak systolic blood pressure by Doppler was 68 to 104 mmHg (mean 86·7 ± 11·9 mmHg). The derived pressure constant, K, from this group ranged from 183 to 265 mmHg (mean 216·7 ± 21·9 mmHg).

The echocardiographic data from the aortic stenosis patients (group 2) are shown in Table 2, and the data are compared in Table 3. End-diastolic wall thickness ranged from 0·42 to 0·64 cm (mean 0·51 ± 0·08 cm), and end-systolic wall thickness ranged from 0·70 to 1·17 cm (0·93 ± 0·21 cm). Both measurements were significantly greater than those in the control group ($p < 0{\cdot}01$). End-diastolic cavity dimension and end-systolic cavity dimension did not vary significantly from group 1 ($p > 0{\cdot}5$, and $p > 0{\cdot}2$, respectively). Relative wall thickness was greater in group 2, with a range of 0·56 to 1·03 cm (mean 0·75 ± 0·19 cm). Percentage wall thickening ranged from 32 to 140 per cent (mean 83·4 ± 41%),

Table 1 *Control group*

Case no.	*Age*	*Weight (kg)*	*Wd (cm)*	*Ws (cm)*	*Dd (cm)*	*Ds (cm)*	*Ws/Ds*	*%WT*	*%SF*	*BPs (mmHg)*	*K (mmHg)*
1	11 mth	10·5	0·40	0·67	2·80	1·70	0·39	68	39	85	216
2	6 wk	4·3	0·31	0·60	2·10	1·50	0·40	48	29	84	210
3	2 mth	4·5	0·35	0·60	1·90	1·15	0·52	71	39	104	199
4	2 mth	4·2	0·35	0·55	2·10	1·40	0·39	57	33	86	219
5	2 mth	4·6	0·30	0·50	2·15	1·25	0·40	67	42	88	220
6	4 mth	5·3	0·35	0·55	2·10	1·40	0·39	57	33	72	183
7	2 mth	4·8	0·34	0·65	2·10	1·45	0·45	89	31	100	223
8	1 mth	3·6	0·24	0·41	1·97	1·36	0·30	71	31	80	265
9	6 mth	6·4	0·41	0·75	2·36	1·51	0·50	83	36	100	201
10	2 mth	4·0	0·22	0·47	2·20	1·60	0·29	114	27	68	231

Wd, end-diastolic wall thickness; Ws, end-systolic wall thickness; Dd, end-diastolic left ventricular dimension; Ds, end-systolic left ventricular dimension; BPs, peak systolic blood pressure by Doppler; %SF, % shortening fraction; %WT, % wall thickening in systole.

Table 2 *Aortic stenosis group*

										Ao-Ps	*LV-Ps*		*ΔP-Ps*	
Case no.	*Age*	*Weight (kg)*	*Wd (cm)*	*Ws (cm)*	*Dd (cm)*	*Ds (cm)*	*Ws/Ds*	*%WT*	*%SF*	*mmHg*	*mmHg Cath*	*Echo*	*mmHg Cath*	*Echo*
1	11 mth	10·4	0·63	1·17	2·75	1·46	0·80	86	47	80	190	174	110	95
2	2 wk	4·5	0·53	0·70	1·72	1·25	0·56	32	27	55*	122	122	67	67
3	1 mth	4·5	0·51	0·81	1·58	0·79	1·03	59	50	100	210	222	110	122
4	7 mth	7·9	0·47	1·13	2·75	1·47	0·77	140	47	100	150	167	50	67
5	8 mth	8·2	0·42	0·84	2·71	1·48	0·57	100	45	90	100	123	10	33

Wd, end-diastolic wall thickness; Ws, end-systolic wall thickness; Dd, end-diastolic left ventricular dimension; Ds, end-systolic left ventricular dimension; %WT, per cent wall thickening in systole; %SF, per cent shortening fraction; Ao-Ps, peak systolic aortic pressure during cath or (*) by Doppler (mmHg); LV-Ps, peak systolic left ventricular pressure, in mmHg, during cath and predicted by echo; ΔP-Ps, peak systolic pressure difference between LV and Ao (mmHg) during catheterisation and predicted by echocardiogram.

and was not significantly different from group 1.

Shortening fraction was increased for group 2, ranging from 27 to 50 per cent (mean 43·2 ±9·2%). The youngest infant, with clinical evidence of congestive heart failure and a large left-to-right atrial shunt at catheterisation, had a normal shortening fraction of 27 per cent, while an asymptomatic infant with only a 10 mm peak systolic pressure difference had an abnormal shortening fraction of 45 per cent.

Peak systolic aortic pressure at catheterisation ranged from 55 to 100 mmHg, measured by indwelling arterial line or Doppler (case 2). Simultaneous left ventricular peak systolic pressure ranged from 100 to 210 mmHg. Using the pressure constant derived from group 1 (K = 217 mmHg), estimated left ventricular peak systolic pressure ranged from 123 to 222 mmHg. Excellent correlation ($r = 0·94$) was found between directly measured peak left ventricular pressure and estimated peak pressure (Fig. 2). The peak systolic pressure difference across the aortic valve measured at catheterisation ranged from 10 to 110 mmHg, while the pressure difference predicted by echo

Table 3

		Wd (cm)	*Ws (cm)*	*Dd (cm)*	*Ds (cm)*	*Ws/Ds*	*%WT*	*%SF*
Group 1 Control	Mean	0·33	0·58	2·18	1·43	0·40	72·5	34
	±SD	0·06	0·10	0·25	0·16	0·07	19·0	4·9
Group 2 Aortic stenosis	Mean	0·51	0·93	2·30	1·29	0·75	83·4	43·2
	±SD	0·08	0·21	0·60	0·30	0·19	41·0	0·2
	p	<0·01	<0·01	>0·5	>0·2	<0·01	>0·4	<0·05

p value compares group 1 and group 2; SD, standard deviation. Other abbreviations as in Table 1.

ranged from 33 to 122 mmHg. Again, excellent correlation (r = 0·95) was noted (Fig. 3).

Discussion

Non-invasive assessment of the degree of aortic stenosis has been generally unreliable. While the scalar electrocardiogram may indicate increased left ventricular forces as well as ST segment depression and T wave inversion in the paediatric patient with critical aortic stenosis, a normal resting electrocardiogram may be found in children with a significant peak systolic pressure difference, and show minimal change despite progressive obstruction.[6–8] While some investigators report the addition of stress electrocardiography and vectorcardiography aided in the detection of moderately severe aortic stenosis, other studies have been less conclusive.[9–12]

Single crystal echocardiographic determination of left ventricular dimensions has afforded a reliable and reproducible technique in assessing the degree of left ventricular pressure resulting from valvar obstruction in children and adults. Johnson *et al.* initially used shortening fraction as a predictor of the severity of aortic stenosis.[13] In the present series, the shortening fraction, while abnormal for group 2 as a whole, was not as discriminating a predictor of severity of obstruction in these infants as has been reported in older children.

As noted by Bennett *et al.* and re-emphasised by Glanz *et al.*, derivation of the wall stress constant is based on the observation that left ventricular wall mass will proportionately increase in response to a pressure load until wall stress is normalised, and that systolic stress measurements are more sensitive than diastolic measurements in detecting hypertrophy. For these observations to remain valid, ventricular function must remain normal. In Bennett's adult series, when congestive heart failure was present, severity of obstruction could not be accurately predicted. In Blackwood's group of children, those with myocardial failure were excluded from the study.

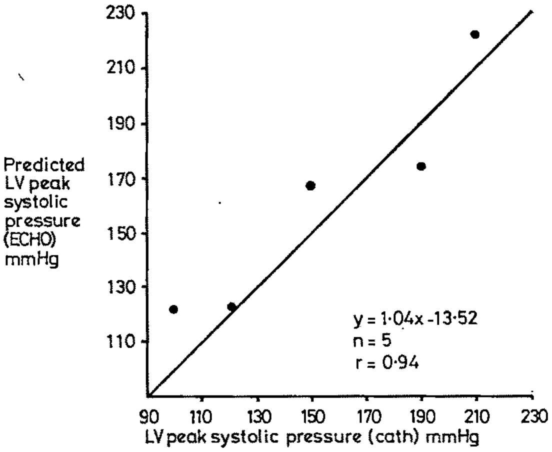

Fig. 2 *Comparison of left ventricular (LV) peak systolic pressure obtained at cardiac catheterisation (cath) with that estimated from echocardiographic data (echo) in five infants with aortic stenosis. Excellent correlation (r = 0·94) is noted.*

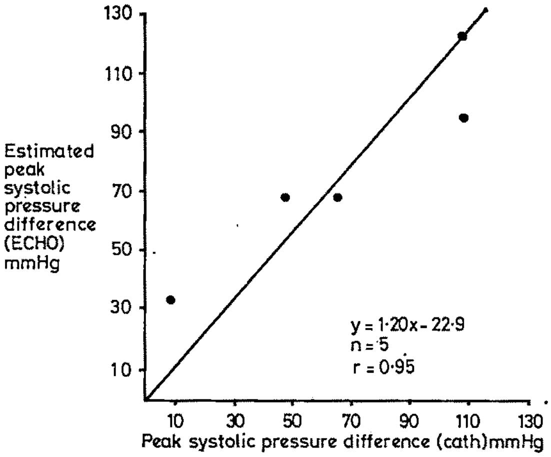

Fig. 3 *Comparison of peak systolic pressure difference obtained at cardiac catheterisation (cath) with that estimated from echocardiographic data (echo) in five infants with aortic stenosis. Excellent correlation (r = 0·94) is noted.*

Two infants in the present series were felt to be in congestive heart failure. In case 2, while the shortening fraction was not increased and did not suggest significant obstruction, the echo measurement of relative wall thickness indicated severe valvular stenosis. In case 3, both shortening fraction and peak predicted pressure indicated severe obstruction.

One can postulate that the reliability of the wall stress index in these two infants is dependent upon the reduction of left ventricular preload by left atrial dilatation and subsequent left-to-right atrial shunt through the foramen ovale. This allows left ventricular function to remain on the ascending limb or peak of the length-tension curve. Thus, as long as there is a "blow-off" for the volume presented to the left ventricle, ventricular dynamics and cardiac output can be maintained and the index is valid. If a left-to-right atrial shunt is not present, or if the resulting combined pressure load to the left ventricle and volume load to the right ventricle exceeds the oxygen demands of the myocardium, caution should be exercised in applying the wall stress index, since cardiac dilatation would lead to underestimation of peak left ventricular systolic pressure.

In summary, these data indicate that the echocardiographic determination of relative wall thickness in infancy allows the most accurate prediction of peak left ventricular pressure and peak systolic pressure differences across an obstructed valve. In patients with aortic stenosis, the technique is ideally suited as a screening device and for serial assessment of increasing pressure difference with age. It should prove useful in selecting a suitable time for cardiac catheterisation and in follow-up management of these patients.

References

1 Bennett DH, Evans DW, Raj MVJ. Echocardiographic left ventricular dimensions in pressure and volume overload: their use in assessing aortic stenosis. *Br Heart J* 1975; **37:** 971–7.

2 Glanz S, Hellenbrand WE, Berman MA, Talner N. Echocardiographic assessment of the severity of aortic stenosis in children and adolescents. *Am J Cardiol* 1976; **38:** 620–5.

3 Blackwood RA, Bloom KR, Williams CN. Aortic stenosis in children: experience with echocardiographic prediction of severity. *Circulation* 1978; **57:** 263–8.

4 Gewitz MH, Werner JC, Kleinman CS, Hellenbrand WL, Talner N. Role of echocardiography in aortic stenosis: pre- and postoperative studies. *Am J Cardiol* 1979; **43:** 67–73.

5 Bass JL, Einzig S, Hong CY, Moller JH. Echocardiographic screening to assess the severity of congenital aortic valve stenosis in children. *Am J Cardiol* 1979; **44:** 82–7.

6 Ongley PA, Nadas AS, Paul MH, *et al.* Aortic stenosis in infants and children. *Pediatrics* 1958; **21:** 207–20.

7 Reynolds JL, Nadas AS, Rudolph AM, Gross RE. Critical congenital aortic stenosis with minimal electrocardiographic changes. *N Engl J Med* 1960; **262:** 276–82.

8 Friedman WF, Modlinger J, Morgan JR. Serial hemodynamic observations in asymptomatic children with valvular aortic stenosis. *Circulation* 1971; **43:** 91–8.

9 Halloran KH. The telemetered exercise electrocardiogram in congenital aortic stenosis. *Pediatrics* 1971; **47:** 31–9.

10 Hugenholtz PG, Lees MM, Nadas AS. The scalar electrocardiogram, vectorcardiogram and exercise electrocardiogram in the assessment of congenital aortic stenosis. *Circulation* 1962; **26:** 79–91.

11 Gamboa R, Hugenholtz PG, Nadas AS. Comparison of electrocardiograms and vectorcardiograms in congenital aortic stenosis. *Br Heart J* 1965; **27:** 344–54.

12 Reeve R, Kawamata K, Selzer A. Reliability of vectorcardiography in assessing the severity of aortic stenosis. *Circulation* 1966; **34:** 92–9.

13 Johnson GL, Meyer RA, Schwartz DC, Korfhagen J, Kaplan S. Left ventricular function by echocardiography in children with fixed aortic stenosis. *Am J Cardiol* 1976; **38:** 611–9.

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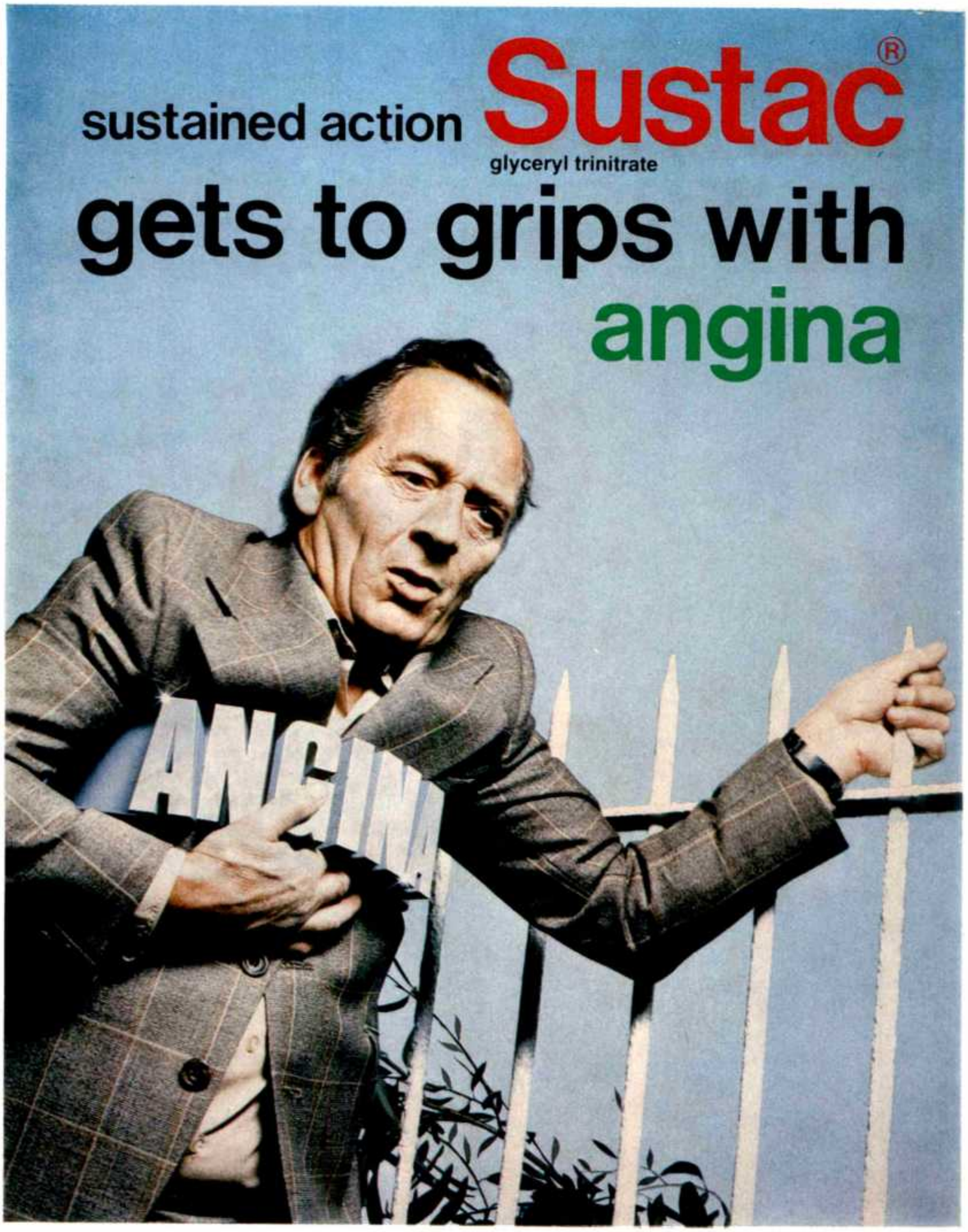

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Br Heart J 1980; **44:** 411–5

Blood pressure and effect of exercise in children before and after surgical correction of coarctation of aorta

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SUMMARY Systolic blood pressure was measured at rest and during exercise in 43 children who had undergone operation for correction of coarctation of the aorta, five children awaiting surgery for coarctation, and 22 control children. Ages ranged from 2 to 15 years, mean 7·6 years.

The mean blood pressure of children with coarctation in both the pre- and postoperative groups was significantly higher at rest than in the controls. Of 43 postoperative patients, 15 (35%) were hypertensive (systolic blood pressure more than 95th centile), and 12 of these had a gradient between the upper and lower limb. Seven of the 28 normotensive patients also had a gradient postoperatively.

Exercise increased the blood pressure more in children with coarctation than in controls, but there was much individual variability and this difference was not significant. Some children with coarctation developed very high blood pressures on exercise, but this was not related to the presence of a gradient.

The mean interval after operation was significantly shorter in the hypertensive group, independent of the age at operation.

Hypertension with or without a gradient commonly persists despite apparent successful surgical correction, but exercise is of limited value in its assessment in this age group.

It has been shown that there is a significant incidence of premature death in patients surviving operation for coarctation of the aorta, and that cardiovascular disease is the primary cause of these deaths.[1] Hypertension has been established as a major risk factor for cardiovascular disease,[2] and persistence of hypertension after repair of coarctation is likely to be an important factor in these deaths.

The hypertension after resection of coarctation may be in the upper limb only and associated with a gradient between upper and lower limbs, or it may be generalised, that is present in both upper and lower limbs without a gradient. The measurement of blood pressure during exercise may be a more sensitive method of detecting hypertension after operation, also reflecting blood pressure levels during normal activities more accurately than measurements at rest.[3 4] We have therefore measured upper and lower limb pressures in children with previously resected coarctation, some of whom were hypertensive, and have investigated the effect of exercise on the upper limb pressure.

Subjects and methods

Studies were made of 48 children with coarctation, 29 boys and 19 girls, aged 2 to 15 years. Of these, 43 had had previous surgical repair of their coarctation, and the result had been considered satisfactory. Three patients had had operations in infancy, and now required further operation for recoarctation which had been confirmed at cardiac catheterisation. Two patients who were newly diagnosed were studied before operation. Twenty-two normal children aged 2 to 12 years were used as controls. These were healthy sibs of patients, or relatives of hospital staff.

Seven of the children had other cardiac lesions in addition to coarctation: two had ventricular septal defect (one with the pulmonary artery

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banded), two had aortic valve disease, one had mitral valve disease, one had complex cyanotic congenital heart disease, and one had had a Mustard operation. Two of the children were taking antihypertensive drugs at the time of study. The age at operation ranged from 7 days to 168 months (mean 20 months), and the length of postoperative follow-up ranged from one month to 144 months (mean 73 months).

Measurements were made using the Parks Doppler ultrasound system[5] and a random zero sphygmomanometer.[6] The upper limb blood pressure was measured using a cuff with an inflation bladder 7·6 cm wide and 15·5 cm long for arms with a circumference of 22 cm or less, and with an inflation bladder 12·5 cm wide and 22·5 cm long for arms with a circumference greater than 22 cm. The relation of these cuffs to arm size has previously been evaluated.[7] A 12 cm cuff was used to measure all blood pressures in the leg, as all leg circumferences were greater than 22 cm. Measurements were made in triplicate, and the mean subsequently analysed. The children's weight, maximum arm and leg circumference, and any drug treatment were recorded. The blood pressure was recorded in the right arm sitting, and then in the right leg while the child was sitting with the leg stretched out horizontally. The sitting position was used because we found that younger children were unco-operative when made to lie down for blood pressure measurements. The patients then exercised for three minutes, after which the blood pressure was measured in the right arm with exercise continuing until the measurements were completed. The heart rate was recorded continuously using chest electrodes and an electrocardiographic monitor.

Children aged 7 years and over exercised on a bicycle ergometer with a work load of approximately two watts/kilo body weight, and 60 to 70 pedal revs/minute. The work load was adjusted so that the heart rate remained over 150/minute during exercise. Children younger than 7 exercised on a treadmill, the slope of which was kept at 20 per cent, and the speed increased until the heart rate remained over 150/minute. This heart rate was chosen because it occurs at a work load of approximately half the child's physical working capacity[8] and represents a submaximal exercise level.

A blood pressure gradient was arbitrarily defined as a difference of more than 5 mmHg between the upper and lower limb. We defined hypertensive subjects as those with a systolic blood pressure above the 95th centile for blood pressure as defined by the American task force for blood pressure control in children.[9]

All values have been quoted as means ±SD. The mean values have been compared by Student's t test.

Results

(1) BLOOD PRESSURE AT REST

Fifteen (35%) of the 43 postoperative patients were hypertensive at rest (see Fig. 1); of these, three had systolic hypertension without a gradient, and 12 had a gradient between the upper and lower limb. The gradient varied from 9 to 38 mmHg, mean 20 mmHg. Seven of the normotensive postoperative patients also had blood pressure gradients between the upper and lower limb, and this ranged from 6 to 28 mmHg, mean 14 mmHg. Four of the five patients studied preoperatively (two with recoarctation and two new patients), had upper limb pressures above the 95th centile. One of the five had an unrecordable lower limb blood pressure: the gradient in the other four patients ranged from 26 to 41 mmHg, mean 35 mmHg.

None of the control group was hypertensive (Fig. 1) and values for resting blood pressures in this group corresponded to previously published data for blood pressure in this age group.[9] None of the control group had a gradient between the upper and lower limb.

(2) BLOOD PRESSURE DURING EXERCISE

Fig. 2 and the Table show blood pressure during exercise and at rest in preoperative, postoperative, and control groups. The mean blood pressure was

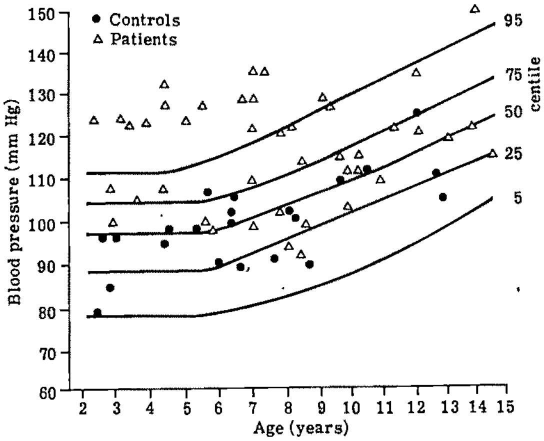

Fig. 1 *Upper limb systolic blood pressures of controls and patients with coarctation postoperatively, measured at rest. Centiles taken from report of task force on blood pressure.*[9]

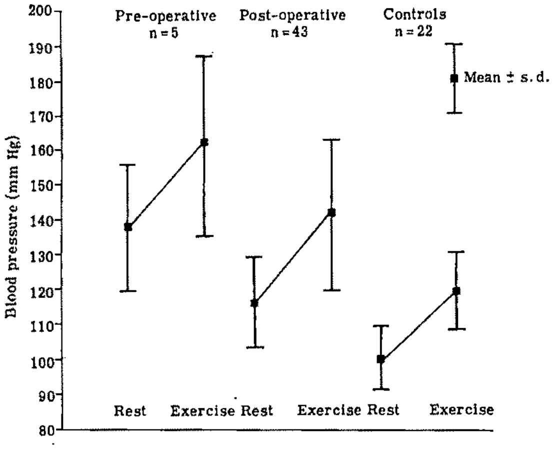

Fig. 2 *Mean increase in blood pressure on exercise in patients with coarctation, before and after operation, and in controls.*

highest, as expected, in the preoperative group, but was also significantly higher than in the controls in the postoperative group, both at rest and during exercise ($p < 0{\cdot}001$).

Upper limb systolic pressure increased on exercise in all the children. The mean increase in blood pressure in children with coarctation was 25 mmHg, but this was not significantly more than in controls, where the mean rise on exercise was 21 mmHg (Table). The mean increases in the hypertensive postoperative group, and in the preoperative group were 24 and 25 mmHg, respectively. The presence of hypertension therefore did not significantly alter the blood pressure response to exercise in these children. Persistence of a gradient between upper and lower limb pressures did not affect the rise in blood pressure on exercise either, as the mean rise in blood pressure in the children with gradients was 21 mmHg.

Two children developed very high blood pressures during exercise—increases of 50 and 80 mmHg. One of these was hypertensive without a gradient, the other was normotensive.

We were unable to relate the presence of hypertension to age at operation, though the interval since operation was significantly shorter in the hypertensive group, independent of age at operation. The mean interval since operation of the hypertensive children was 53 ±30 months, whereas for the normotensive postoperative group it was 80 ±37 months ($p < 0{\cdot}01$).

Discussion

We have confirmed other studies which have shown that hypertension remains a considerable problem in children after operation for coarctation[10–12] and that these children have higher blood pressures than controls during exercise as well as at rest.[13] It is likely that this hypertension contributes to the increased incidence of early deaths from cardiovascular disease in these patients. The high incidence of hypertension after operation that we found was not the result of the artificial circumstances of the hospital environment, since the blood pressures of controls, also measured in hospital, were in the normal range.

We found that one-third of our patients were hypertensive. This is a slightly smaller proportion than reported by Maron *et al.*[1] who found that 37 per cent of postoperative patients were hypertensive 11 to 25 years later, though these authors defined hypertension as exceeding the 90th rather than the 95th centile. Nanton and Olley[10] reported that 24 per cent of patients operated on in childhood remained hypertensive at least six months after operation. An earlier study of 87 patients from this department[14] found that the overall incidence of hypertension after operation was 31 per cent. This study also suggested that the incidence of hypertension without a gradient was lower in the group operated on before 1 year than in those operated on later. In this study there were only three such

Table *Upper limb mean resting blood pressure (mmHg ± SD) and effect of exercise*

	No.	*Blood pressure at rest*	*Blood pressure during exercise*	*Blood pressure rise on exercise*
Control	22	100 ±10	122 ±14	21 ±11
Preoperative	5	138 ±18	163 ±25	25 ±14
Postoperative:				
Hypertensive postoperative	15	130 ±7	154 ±17	24 ±12
Postoperative + gradient	19	125 ±9	146 ±14	21 ±10
Total postoperative*	43	117 ±13	143 ±21	25 ±11

* Nine postoperative patients were neither hypertensive nor had a gradient.

hypertensive patients without a gradient, too small a number for valid comparison.

Twelve of our hypertensive patients had a gradient between the upper and lower limb. Opinions differ as to the degree of gradient that is significant. Eshaghpour and Olley[11] suggested that recatheterisation was indicated in any child with a gradient of more than 10 mmHg, and Maron *et al.*[1] also suspected "residual coarctation" in those with this gradient. Using these criteria 15 of our patients (10 of whom were also hypertensive) needed further study. Since in the normal child by the age of 1 year the blood pressure in the leg, measured by the same technique, is already higher than in the arm,[15] it might be argued that those children who have any gradient have some degree of residual coarctation or have recoarctation, though the significance of this in terms of the circulation is not known. In our patients, those with larger gradients also tended to be hypertensive, that is 10 out of 15 patients with gradients greater than 10 mmHg. The gradients reported here are underestimates of the true gradient since we made measurements on the leg with the children sitting. In this position blood pressure in the leg is increased as a result of the hydrostatic effect of a column of blood between the heart and the cuff, and the true leg pressure is therefore lower.

The incidence of hypertension without a gradient in the postoperative patients studied was 7 per cent and was lower than in other series, but more hypertensive patients with a gradient (28%) were found. Nanton and Olley[10] in their series found that 24 per cent of children remained hypertensive after operation, and that this was associated with a gradient in 11 per cent and not associated with one in 15 per cent.

The value of exercise in the assessment of these children is doubtful. Though the mean rise in blood pressure on exercise was greater in those children with coarctation, particularly if they were hypertensive, this difference was not statistically significant, and there was considerable variation. This is shown by the greater standard deviation of exercise blood pressure (14 to 25 mmHg) compared with resting blood pressure (7 to 18 mmHg). Part of this increase in variability is a result of the difficulties of blood pressure measurement during exercise. Freed *et al.*[16] showed a significantly greater rise in blood pressure after "exercise to exhaustion" in 30 postoperative patients, and it is possible that more strenuous exercise levels would have shown a greater blood pressure rise in our patients. The population studied by Freed *et al.*, however, was considerably older than ours, as the mean age was 14 years and the youngest patient was aged 6, whereas the mean age of our study group was 7·6 years and 13 patients were aged 6 or under. The rise in blood pressure on exercise was not related to the presence of a gradient at rest. Freed *et al.*[16] and Connor[17] have shown that the gradient between the upper and lower limb rose after exercise, and Connor has subsequently recommended recatheterisation in some patients on the basis of the postexercise gradient. In our opinion it is not possible to record blood pressure, with any accuracy, when the child had stopped exercising as our experience has shown that it starts to fall the instant exercise stops. This view is held by others.[18 19] Connor states that he measured blood pressure in the leg before the arm after exercise so as to underestimate any increase in gradient that might occur because of decrease in heart rate and cardiac output "in 30 to 45 seconds between measurements". Cumming *et al.*[20] showed that heart rate in children fell from 200 to 120 beats/minute within two minutes of stopping exercise, indicating again that measurements made during recovery from exercise are rapidly changing and inaccurate. We did not study enough children both before and after operation to show whether the rise in blood pressure which occurs preoperatively will predict the effect of surgery on the blood pressure. Our previous experience with exercise tests in a group of children under 6 has shown that attempting more strenuous exercise levels only leads to lack of co-operation. We have been unable to find any published data on exercising very young children and therefore we used Godfrey *et al.'s* criteria[8] of heart rates for submaximal exercise to produce some standardisation of exercise levels. It is, thus, possible that exercising older children who are better able to co-operate and to exercise them to exhaustion may be helpful in the evaluation of the postoperative patient.

It has been shown that exercise blood pressures give a better indication of the blood pressure during normal activities in adults than casual resting measurements,[3 4] and our results did show that two children who were normotensive or mildly hypertensive at rest, developed very high blood pressures during exercise. It is possible that these children should be taking antihypertensive treatment, since cardiovascular complications could be associated with peak rather than resting blood pressure. In fact, only two children were actually receiving treatment, and this may reflect the inaccuracy of pressure measurement or, more likely, a general reluctance to treat hypertension in children especially if it is mild.

Measurement of blood pressure soon after operation was associated with a greater incidence of hypertension. This suggests that the blood pressure may cross centiles and stabilise within normal limits, even if the child remains hypertensive for some months after surgery. Further analysis based on retrospective study of blood pressure recorded in the hospital case notes was not possible, because of inaccurate and varied blood pressure recording techniques. It is possible that the apparent decrease in incidence of hypertension with time occurs because some patients who were lost to follow-up were relatively hypertensive, and some may have died early in the follow-up period because of hypertension. A prospective study is necessary to evaluate these possibilities. Differing surgical techniques are unlikely to account for this observation, as all children studied had a similar operative technique, that is end-to-end anastomosis rather than aortoplasty.

In conclusion, hypertension both with and without a gradient persists in up to one-third of patients after corrective surgery for coarctation, but the usefulness of exercise testing in assessing this in young children is limited by the degree of variation in the individual's blood pressure response to exercise. There may be some value in detecting those children who, though only mildly hypertensive at rest, develop very high blood pressures on exercise.

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References

1 Maron BJ, Humphries JO, Rowe RD, Mellits ED. Prognosis of surgically corrected coarctation of the aorta. *Circulation* 1973; **47:** 119–26.

2 Kannel WB. Some lessons in cardiovascular epidemiology from Framingham. *Am J Cardiol* 1976; **37:** 269–82.

3 Millar Craig M, Raftery EB. The response to exercise in hypertensive subjects. *Clin Sci Mol Med* 1978; **54:** 18–19.

4 Hamer J, Fleming J, Shinebourne E. Effect of walking on blood pressure in systemic hypertension. *Lancet* 1967; **ii:** 114–8.

5 Elseed AM, Shinebourne EA, Joseph MC. Assessment of techniques for measurement of blood pressure in infants and children. *Arch Dis Child* 1973; **48:** 932–6.

6 Wright BM, Dore CF. A random-zero sphygmomanometer. *Lancet* 1970; **i:** 337–8.

7 de Swiet M, Fayers P, Shinebourne EA. Systolic blood pressure in a population of infants in the first year of life—The Brompton study. *Pediatrics* 1980 **65:** 1028-35.

8 Godfrey S, Davies CTM, Wozniak E, Barnes CA. Cardio-respiratory response to exercise in normal children. *Clin Sci* 1971; **40:** 419–31.

9 National Heart, Lung, and Blood Institute. Report of the task force on blood pressure control in children. *Pediatrics* 1977; **59:** 797–8.

10 Nanton MA, Olley PM. Residual hypertension after coarctectomy in children. *Am J Cardiol* 1976; **37:** 769–72.

11 Eshaghpour E, Olley PM. Recoarctation of the aorta following coarctectomy in the first year of life: a follow-up study. *J Pediatr* 1972; **80:** 809–14.

12 Liberthson RR, Pennington DG, Jacobs ML, Daggett WM. Coarctation of the aorta: review of 234 patients and clarification of management problems. *Am J Cardiol* 1979; **43:** 835–40.

13 James FW, Kaplan S. Systolic hypertension during submaximal exercise after correction of coarctation of aorta. *Circulation* 1974; **49** & **50,** suppl II: 27–34.

14 Shinebourne EA, Tam ASY, Elseed AM, *et al.* Coarctation of the aorta in infancy and childhood. *Br Heart J* 1976; **38:** 375–80.

15 Moss AJ, Liebling W, Adams FH. The flush method of determining blood pressures in infants. II Normal values during the first year of life. *Pediatrics* 1958; **21:** 950–7.

16 Freed MD, Rocchini A, Rosenthal A, Nadas AS, Castaneda AR. Exercise-induced hypertension after surgical repair of coarctation of the aorta. *Am J Cardiol* 1979; **43:** 253–8.

17 Connor TM. Evaluation of persistent coarctation of aorta after surgery with blood pressure measurement and exercise testing. *Am J Cardiol* 1979; **43:** 74–8.

18 Godfrey S. *Exercise testing in children.* London: WB Saunders, 1974.

19 Sannerstedt R. Haemodynamic response to exercise in patients with arterial hypertension. *Acta Med Scand* 1966, suppl 458: 11.

20 Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. *Am J Cardiol* 1978; **41:** 69–75.

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Predictive value of ST segment elevation in cardiac pacing

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SUMMARY In 366 pacemaker patients the influence of intracardiac ST segment elevation on the fate (displacement or perforation) of permanent cardiac pacemaker electrodes was studied.

In one group of patients a retrospective analysis was carried out, the operator being aware of the degree of ST segment elevation and positioning the electrode to avoid very high or very low values wherever possible. In the second group a prospective trial was carried out. The final electrode position was determined solely by fluoroscopy and electrical threshold, and the ST segment shift measured afterwards.

The combined rates of electrode displacement and perforation did not differ between these groups. High levels of ST segment elevation, greater than 10 mV, were found to predispose to electrode perforation. On the other hand, low ST segments did not predict a displacement. It is concluded that the ideal positioning technique should seek a low electrical threshold, a stable position, and avoid high ST elevation.

The intracardiac electrocardiogram recorded via a pacemaker electrode varies according to the position of the electrode tip, and has been used to position temporary electrodes in the right ventricle when *x*-ray screening facilities are not available,[1] or to aid correct positioning of the electrode for long-term pacing.[2–4]

In this study the spontaneous intracardiac electrocardiogram was analysed, not an evoked response. Both the QRS complex and the ST segment can be of assistance, and in this study we have concentrated on the latter (Fig.). ST segment elevation occurs when the electrode tip comes into contact with the ventricular endocardium, and is a result of the "current of injury".[2] It varies from 0·6 to 15·0 mV and falls with time.[2] With impending perforation the ST segment elevation increases, and on perforation the ST segment becomes isoelectric, with T wave inversion.[5] It has been suggested that an optimal ST segment elevation of 2 to 8 mV should be sought during insertion, since lower values might be followed by electrode displacement[6] and higher ones by electrode perforation,[3 7 8] though few substantiating data have been published.

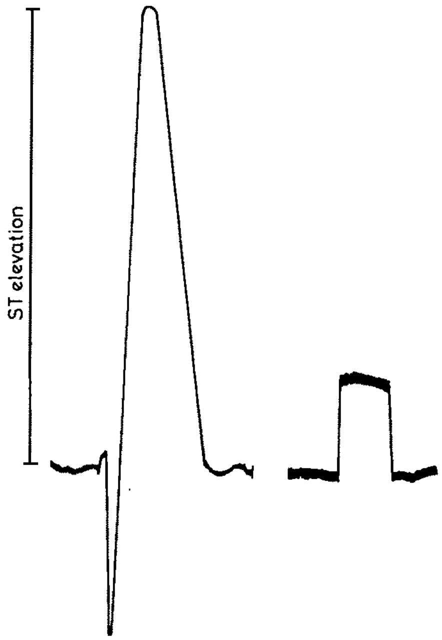

Fig. *The spontaneous intracardiac electrocardiogram, showing the measurement of the ST segment elevation together with a one millivolt calibration wave.*

Materials and methods

The study was divided into two parts, the first

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being a retrospective study of 163 pacemaker implantations (group 1). In these cases the final electrode position was partly determined by the intracardiac electrocardiogram. If the ST elevation was very high or very low the electrode position was moved in an attempt to achieve a more moderate value, though occasionally it could not be altered. The second part of the study was a prospective one of 203 consecutive insertions (group 2), where the intracardiac electrocardiogram was recorded only after final positioning, which it did not, therefore, influence.

All intracardiac electrocardiograms were recorded by an ultraviolet light recorder (frequency response 650 Hertz) and a permanent trace was kept, together with a 1 mV calibration deflection. The study lasted from January 1977 to July 1979 with a minimum follow-up period of six months for each patient. The implantations were performed by several experienced operators. Several routes of insertion and several electrode types were used, but not modern helical or active fixation electrodes. One type of electrode produced very high failure rates, and the results of those insertions were excluded from the study.

Table 1 *Outcome of pacing in groups 1 and 2*

	Normal		*Displacement*		*Perforation*		*Other complications**	*Total (No.)*
	(No.)	*(%)*	*(No.)*	*(%)*	*(No.)*	*(%)*	*(No.)*	
Group 1 retrospective n=163	129	79·1	8	4·9	11	6·7	15	163
Group 2 prospective n=203	178	87·7	13	6·4	7	3·4	5	203

* Including fractured electrodes, elevated thresholds, and pacemaker cavity infections.

The electrocardiograms were analysed for the height of the ST elevation, and for the shape of the T wave. The ST elevation found was allocated into three subgroups, 0 to 4·9 mV, 5 to 9·9 mV, and greater than 10 mV. These, and the shape of the T wave, were then compared with the outcome of the pacemaker implantation, and the results tested for statistical significance by the χ^2 test.

Results

The overall rates of displacement and perforation in groups 1 and 2 are shown in Table 1. ST elevation tended to be lower in group 2 (group 1, mean 7·33, SD ±3·5; group 2, mean 5·76, SD ±3·81, p < 0·001).

Table 2 *Effect on outcome on ST elevation*

		ST elevation					
		0 to 4·9		*5 to 9·9*		*10→*	
	Group	*(No.)* *n=121*	*(%)*	*(No.)* *n=186*	*(%)*	*(No.)* *n=59*	*(%)*
Normal	1	22		84		23	
	2	85		69		24	
	Total	107	88·4	153	82·3	47	79·6
Displacement	1	1		6		1	
	2	6		5		2	
	Total	7	5·8	11	5·9	3	5·1
Perforation	1	0		6		5	
	2	1		2		4	
	Total	1	0·8	8	4·3	9	15·2
Other*	1	3		12		0	
	2	3		2		0	
	Total	6	5	14	7·5	0	0

* See footnote to Table 1.

Though there was a lower rate of perforation and a higher rate of displacement in group 2 compared with group 1, these differences were not significant. The combined rates of perforation and displacement were similar in the two groups. Other complications, such as electrode fracture, were commoner in group 1, where the follow-up period was slightly longer (group 1, mean 23·1 months; group 2, mean 18·4 months).

The outcome of pacemaker implantation is related to the height of ST elevation in Table 2. The relation of ST elevation to displacement was not significant, but there was a strong positive correlation between raised ST elevation and perforation (p < 0·001).

In Tables 3 and 4 the presence of T wave inversion was matched with the degree of ST elevation, and with the outcome of pacing, and it was clear that there was no strong association. Both high and low ST elevation were more often associated with T wave inversion.

When we analysed our data in different groupings (0 to 2 mV, 2 to 8 mV, 8 mV upwards) our findings were unaltered.

Table 3 *Relation of T wave to ST elevation in prospective study*

ST elevation (mV)	*Upright T*		*Inverted T*		*Isoelectric T*	
	(No.)	*(%)*	*(No.)*	*(%)*	*(No.)*	*(%)*
0–4·9 n=95	34	35·7	40	42·1	21	22·1
5–9·9 n=78	34	43·6	14	17·9	30	38·5
10 Plus n=30	7	23·3	9	30	14	46·7

Discussion

Despite advances in pacemaker implantation techniques, the rate of displacement remains at around 10 per cent,[9] and electrode perforation is also a significant problem.[10 11] It is therefore important to minimise these risks by seeking an optimal position of the electrode in the right ventricle. Though some centres measure ST elevation during pacemaker implantation, others do not, and its value has not been fully studied previously.

In group 2 electrode positioning was undertaken in ignorance of the degree of ST elevation, which tended to be lower than in group 1. The overall rate of pacemaker complications (perforation plus displacement) was no higher in this group, despite the fact that the intracardiac electrocardiogram had not been used during positioning.

Table 4 *Relation of T wave to pacemaker outcome in the prospective study*

Pacemaker outcome	*Upright T*		*Inverted T*		*Isoelectric T*	
	(*No.*)	(%)	(*No.*)	(%)	(*No.*)	(%)
Normal* n=183	67	36·6	58	31·7	58	31·7
Displacement n=13	6	46·2	3	23·1	4	30·8
Perforation n=7	2	28·6	2	28·6	3	42·9

* Including five patients with other complications (Table 1).

Higher levels of ST elevation were clearly associated with an increased liability to perforation, but low levels were not associated with an increased liability to displacement as a recent study[6] claimed. These workers described ST elevation of less than 2 mV as unsatisfactory, but the range of ST elevation in their patients with displacement was similar to the range in their normal controls, with no statistical difference being shown.

Intracardiac electrocardiograms should be routinely monitored during implantation of permanent cardiac pacemaker electrodes, since the height of ST elevation is of some predictive value; levels between 0 and 10 mV are acceptable. T wave inversion is of no significance.

I would like to thank Professor P Sleight and Dr D Bennett for their assistance with this study.

References

1 Chatterjee K, Sutton R, Layton CA, Edwards A. The cavity electrocardiogram in emergency artificial pacing. *Postgrad Med J* 1969; **45:** 713–7.

2 Furman S, Hurzeler P, deCaprio V. The ventricular endocardial electrogram and pacemaker sensing. *J Thorac Cardiovasc Surg* 1977; **73:** 258–66.

3 Harris AM. Transvenous pacing. *Br J Hosp Med* 1969; **1:** 1131–5.

4 Gulotta SJ. Transvenous cardiac pacing. Technics for optimal electrode positioning and prevention of coronary sinus placement. *Circulation* 1970; **42:** 701–18.

5 Vera Z, Janzen DA, Awan NA, Mason DT. Perforation of heart by pacemaker electrodes: an experimental study (abstract). *Clin Res* 1976; **24:** 244A.

6 Parsonnet V, Bilitch M, Furman S, *et al.* Early malfunction of transvenous pacemaker electrodes. A three-center study. *Circulation* 1979; **60:** 590–6.

7 Sutton R, Norman J. The cardiac electrogram in demand pacing. In: J Norman, A Rickards, eds. *Proceedings of the pacemaker colloquium.* Dieren: Vitatron Medical, 1976: 178–81.

8 Gialafos J, Kolettis M, Hadjigeorge C, Georgiou V, Avgoustakis D. The significance of intraventricular electrocardiogram in artificial heart pacing. *Acta Cardiol (Brux)* 1975; **30:** 487–97.

9 Brewster GM, Evans AL. Displacement of pacemaker leads—a 10 year survey. *Br Heart J* 1979; **42:** 266–70.

10 Dancy M, Jackson G, Lau OJ, Farnsworth A. Successful treatment of myocardial perforation and tamponade after temporary endocardial pacing. *Br Med J* 1978; **i:** 79–80.

11 Rubenfire M, Anbe DT, Drake EH, Ormond RS. Clinical evaluation of myocardial perforation as a complication of permanent transvenous pacemakers. *Chest* 1973; **63:** 185–8.

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Ambulatory ST segment monitoring

Problems, pitfalls, solutions, and clinical application

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SUMMARY The introduction of frequency modulated recording systems for ambulatory electrocardiographic monitoring (Oxford Medilog mark 2 and Cardiodyne cassette recorders) prompted comparison with a conventional direct recording type of recorder (Oxford Medilog mark 1). The recordings obtained by the frequency modulated recorders were very much superior to those obtained by the direct recording type of recorder. The direct recording suffered from poor low frequency response, phase shift, and cable motions artefacts. Correction of these problems with careful attention to electrode application enabled stable graphs to be obtained over 24 hours. The clinical applications were explored by comparing the results of exercise tests with a computer assisted system with frequency modulated ambulatory monitoring in 30 patients. A range of ST deviations from pure ST depressions throughout 24 hours, pure ST elevation, and a combination of ST elevation and depression were seen, suggesting a spectrum of changes hitherto unsuspected in these patients. Painless ST changes were approximately twice as common as those associated with pain. These findings indicate a valuable role for ST segment monitoring in ischaemic heart disease, particularly with the availability of high fidelity modulated tracings which do not distort ST segments.

Ambulatory monitoring of the electrocardiogram for the detection and quantification of arrhythmias has become an accepted and widely used diagnostic technique.[1–3] High quality recordings can readily be obtained from praecordial electrodes because the shape and temporal relations of the QRS complex are the most important features for arrhythmia analysis. This means that narrow band-width recordings can be safely employed to eliminate artefact and provide a stable baseline. However, narrow band-widths impose limitations on the use of ambulatory tape recordings to monitor ST segment changes which may be significant of myocardial ischaemia, because these electrical events essentially have a low frequency, and the cut-off so essential for stabilising the baseline produces considerable ST distortion. Nevertheless, some workers have used standard direct recording ambulatory tape recorders to detect ST segment shifts, though most have been cautious in interpreting the results in a quantitative fashion.[4–10] The introduction of frequency modulated (FM) recording systems should go a long way towards solving these problems, but the dimensions of artefactual ST alterations and the precision and reproducibility of different commercially available systems have not yet been reported. We have conducted such an investigation and report the results here.

Materials and methods

This investigation was conducted in three parts:

(1) A detailed examination of the electrocardiographic electrode system to identify and correct possible sources of artefact. After considerable experimentation it was recognised that artefacts arose from the skin electrode interface, the movement of loose cables, and at the recorder cable junction. Artefacts arising at the skin electrode interface could be related to the method of skin preparation, muscle movements, electrode jelly stability, and electrode adhesion.

(2) Three tape recorders commonly used for arrhythmia detection were evaluated for detection of ST segment changes:

(a) *Oxford Medilog mark 1* direct recording at 1/60 real time continuously.*

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* Manufactured by Oxford Medical Systems, Abingdon, Oxon.

(b) *Oxford Medilog mark 2* FM recording continuously.* This has two channels for electrocardiogram, one for time signals, and one for event marking. These can be played back at 60 times recording speed.

(c) *Cardiocassette* FM recording at real time.† This recorder has a built in programmer which starts the recorder at preset intervals of 15 minutes to two hours and stops it after five to 30 seconds. At the shortest programme of 15-minute intervals and 30 seconds recording time, a tape lasts 18 hours. It can also be used for continuous recording for one hour and played back on any electrocardiograph at real time.

The frequency characteristics of each machine were assessed by recording 1 mV and 2 mV square wave calibration signals and playing them back into the analyser.

Each recorder was then evaluated by simultaneously recording the electrocardiogram on all three in a total of 20 patients with ischaemic changes on the electrocardiogram during exercise. The standard for comparison was an online digital computer-assisted multichannel exercise system which produced continuous computed values for ST depression/elevation and ST slope‡ (Marquette; CASE). The exercise electrocardiogram was recorded with this system as a standard. The recordings from the Cardiocassette were played back directly via the CASE system. The Medilog mark 1 and mark 2 recordings were converted into real time with suitable flutter compensation and then played back via the CASE system. Reproduction of signals at 1:1 was ensured by the initial calibration markers. The R wave amplitude was measured manually and the ST segments were computed at the J point and the ST slope at a point one-eighth of the RR interval after the J point. Any recordings with high frequency artefacts and isoelectric drift were excluded.

(3) The clinical application of the three tape recorders was assessed in relation to the exercise test. Ambulatory electrocardiograms of 30 patients with positive exercise tests and symptomatic angina were monitored using two bipolar praecordial leads CM5 and CC5. The tapes were played back on an Oxford PB-4 deck into a Reynolds Medical Pathfinder electrocardiographic analyser with an ST segment plotter.§ The plotting module had a zero reference, calibration markers, and two spots which could be positioned on the most horizontal part of the PR segment (isoelectric level) and on the J point of the ST segment. The ST segment plotter estimated the difference in amplitude between these two points, excluding artefacts and ectopic beats. The analogue output of heart rate and ST segments were fed into a linear recorder at a paper speed of 1 cm/hour of real time recording. The ST segment changes were correlated with the exercise test results and the patient diaries. Any ST depression or elevation at least 1 mm below or above the isoelectric line, the total episode lasting at least for six minutes, was defined as abnormal for the purposes of this study.

Results

Electrode sites were chosen over bony sites free of major muscle masses. The manubrium sterni, left sixth rib in the anterior axillary line, and the right sixth rib in the anterior axillary line were chosen as standard sites to give the two bipolar leads CM5 and CC5. The skin over the area was shaved if necessary and cleaned with isopropyl alcohol to remove grease. The electrode sites were then marked with a felt pen and touched with a high speed battery operated burr with an abrasive tip¶ to remove the stained epidermis. This process was entirely painless, unlike brisk rubbing with rough gauze, the method commonly used.

Various commercially available electrodes were tested for stability of the gel and adhesion characteristics. A new electrode, with nickel coated brass as the electrode material and a chloride-free gel isolated in a bubble pack until application, was found to yield stable tracings. It also used a strong non-allergenic adhesive developed for colostomy bags (Roussel Medical Ltd).

Cable movement artefacts were reduced by attaching the preamplifiers to the cables close to the electrodes and applying an elastic porous bandage around the chest to keep the electrodes, preamplifiers, and cables free from movement.

A special connection was designed to fix the cables to the recorders and prevent bending and movement at these sites. These simple measures produced a dramatic improvement in the stability of the isoelectric line (Fig. 1).

RESPONSE TO SQUARE WAVE CALIBRATION

The response to a 1 mV square wave calibration pulse was defined as adequate if it fell within the recommendations of the American Heart Association.[11] The Cardiocassette and Oxford Medilog mark 2 recorder both produced an adequate response at 1 mV and 2 mV levels. On the other hand, the Medilog mark 1 oroduced distortion of the peak of the calibration signal and artefactual depression of the baseline (Fig. 2).

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*Manufactured by Oxford Medical Systems, Abingdon, Oxon.

† Manufactured by Cardiodyne Inc, Cupertino, California, USA.

‡ Marquette Electronics Inc, Milwaukee, Wisconsin, USA.

§ Manufactured by Reynolds Medical Limited, Hertford.

¶ MS Expo Ltd, Sustanum Works, Tichfield, UK.

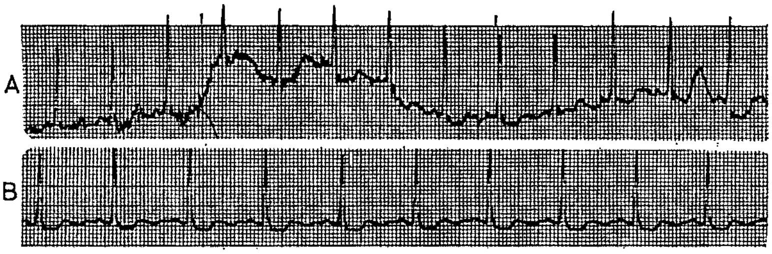


Fig. 1 *The top panel* (A) *shows artefacts commonly seen during ambulatory monitoring. The lower recording* (B) *shows elimination of artefacts by measures described in text.*

R WAVE AMPLITUDE

This was carefully measured particularly because of the renewed interest in R wave amplitude in ischaemic heart disease.[12] Measurements made from recordings using the Cardiocassette and the Medilog mark 2 were consistently within 5 per cent of the standard. The Medilog mark 1 consistently underestimated R wave amplitude by between 10 and 27 per cent (mean ±SEM 19·1±1·0%) (Table 1).

ST SEGMENT CHANGES

The maximal ST segment changes measured with the three recorders were compared with the standard. In 19 out of 20 recordings using the Cardiocassette the measurement was within 0·5 mm of the standard, in 15 it was within 0·2 mm, and in two recordings it was identical with the standard. One recording could not be analysed because of high frequency artefacts.

The Oxford Medilog mark 2 produced recordings in which maximal ST segment change was within 0·5 mm of the standard in 18 and within 0·2 mm in four. Two recordings could not be analysed because of high noise levels.

The Oxford Medilog mark 1 produced six recordings in which measurements were within 0·5 mm of the standard and two recordings within 0·2 mm of the standard. In seven, differences were greater than this, the maximum being 1·2 mm Five recordings could not be analysed because of high frequency artefacts.

ST SLOPE

The ST slope was within 0·5 mV/s of the standard in 12 out of 20 Cardiocassette recordings and within 1·0 mV/s in seven. The Medilog mark 2 produced 10 recordings in which ST slope was within 0·5 mV/s of the standard, and in the rest ST slope was within 1·0 mV/s.

Measurements of ST slope from recordings obtained using the Medilog mark 1 differed from the standard by more than 1·0 mV/s in all recordings. In six cases slopes which were negative were read as positive and in three slopes which were positive were read as negative.

Generally, the tracings obtained from the Cardiocassette were the clearest. Initially the noisiest tracings were those produced by the Medilog mark 2; this was attributed to the replay system and was later corrected. Mark 1 recordings were noise free. Some of the common artefacts seen with mark 1 recordings are shown in Fig. 3.

The clinical applications of an ambulatory

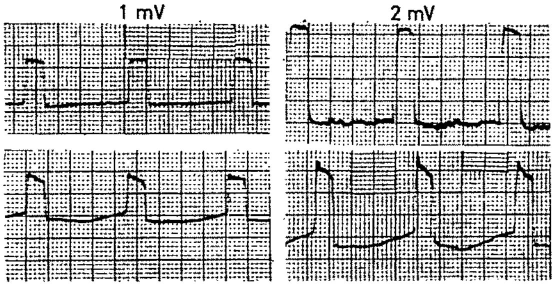


Fig. 2 *Response of Medilog mark 1 DR (lower panels) and mark 2 FM recorders (upper panels) to 1 mV and 2 mV square wave calibration signals. Distortion of the deflection and the baseline is always present in mark 1 recordings.*

Table 1 *Comparison of exercise tests (20 patients)*

	Cardio-cassette	*Medilog mark 2*	*Medilog mark 1*
R wave amplitude (5%)	19	18	0*
Peak ST change (0·5 mm)	19	18	6
Peak ST change (0·2 mm)	15	4	2
ST slope at peak exercise (0·5 mV/s)	12	10	0†
ST slope at peak exercise (1 mV/s)	7	8	0†
Artefacts	1	2	5
Noise level	Nil	+	Nil

* Constant underestimation by 10 per cent.
† All values beyond 1 mV/s.
Figures within parentheses indicate the acceptable variation from the standard.

recording system are to document changes which are not detectable in resting or exercise electrocardiograms and to collect additional information about changes during day and night. Table 2 shows the frequency of ST changes and of episodes of chest pain. The following case reports illustrate the value of ambulatory ST segment monitoring.

Table 2 *Pain and ST changes*

Number of patients monitored	30
Total duration of tapes	612 hours
Exercise test positive	30
Total episodes of pain	61
ST change over 1 mm	194
ST change over 2 mm	112
ST change with normal heart rate	21

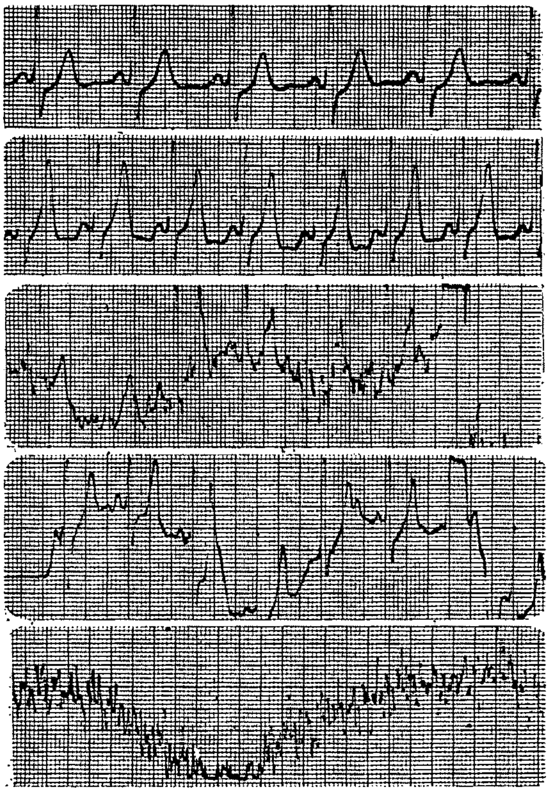


Fig. 3 *Some of the artefacts commonly seen in ambulatory monitoring. The top panel shows a stable resting electrocardiogram. In the second panel an increase in heart rate has produced an increase in the amplitude of T wave and an artefactual depression of the TP segment caused by phase shift. Panels 3 and 4 show artefacts caused by cable-recorder junction movements, and panel 5 those resulting from the electrode jelly drying up.*

Case 1 (Fig. 4)
A 59-year-old male office worker complained of squeezing pain in the neck brought on by exertion and relieved by rest. Treadmill exercise testing produced identical pain accompanied by 4·1 mm ST depression in lead CM5. An ambulatory tape recording showed many episodes of ST depression during a 24 hour period. Moreover, pain in the neck was consistently associated with ST segment depression of 4·0 mm and an increase in heart rate.

Case 2 (Fig. 5)
An electrical engineer complained of recurrent attacks of angina, usually at rest. He was able to exercise for 14 minutes before developing 2·0 mm ST depression. Ambulatory monitoring was performed as the excellent exercise tolerance did not explain the occurrence of frequent angina at rest. The patient developed pain while driving and had four episodes of ST elevation lasting more than 20 minutes each. Coronary arteriography and ^{201}Tl scintigraphy confirmed the presence of critical obstructive coronary artery disease, presumably associated with intermittent spasm.

Case 3 (Fig. 6 and 7)
A 47-year-old woman complained of recurrent chest pain associated with giddiness and occasional blackouts. Repeated exercise tests were normal. Ambulatory monitoring showed six episodes of ST elevation during pain, two with ventricular tachycardia. The patient was treated with verapamil 120 mg t.d.s. and became symptom free within a

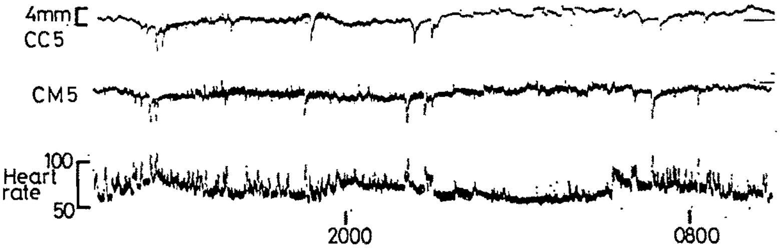


Fig. 4 *Case 1. 24-hour trend chart of ST segment changes in leads CM5 and CC5. The isoelectric line is marked by thin black lines at end of the recording. Only the initial episode of ST change was associated with pain in the neck.*

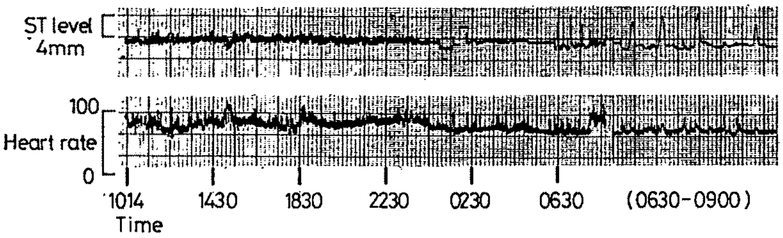


Fig. 5 *Case 2. The 24-hour trend chart shows one episode of ST depression with increased heart rate at 1500 hours and four episodes of ST elevation lasting between three and five minutes after 0630 hours. Only one episode was associated with pain.*

week. Repeated ambulatory monitoring showed no episodes of ST elevation. Coronary arteriograms were normal.

Case 4 (Fig. 8)
A 53-year-old man had had severe angina for two years. His angina was mainly effort related, but recently had occurred also at rest and at night. The exercise test showed 4·0 mm ST depression at 8·0 minutes. Ambulatory monitoring showed episodes of ST depression occurring during the day and the night; on two occasions at night ST elevation preceded ST depression. Coronary arteriograms showed a 90 per cent stenosis of the left main stem; ventricular fibrillation occurred during the procedure but he was successfully resuscitated. A saphenous vein bypass graft operation was performed and the patient was much improved.

Case 5 (Fig. 9)
A 51-year-old woman was attending the outpatient department of the hospital for pain in the left thenar eminence. This pain was brought on by exertion and relieved by rest, but she had also had episodes of similar pain at night. The differential diagnosis before referral to the cardiac department included

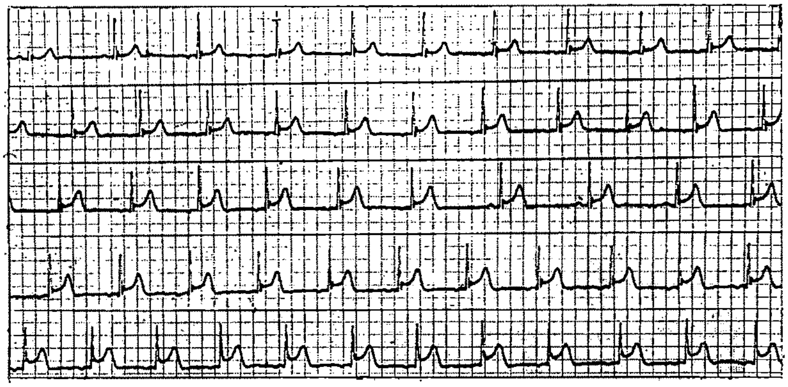


Fig. 6 *Case 3. A continuous tracing in a patient with Prinzmetal's angina. The ST elevation progressively increases within a very short time.*

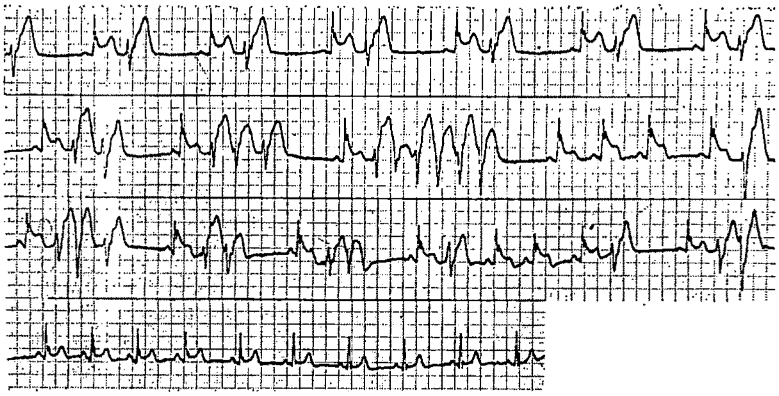
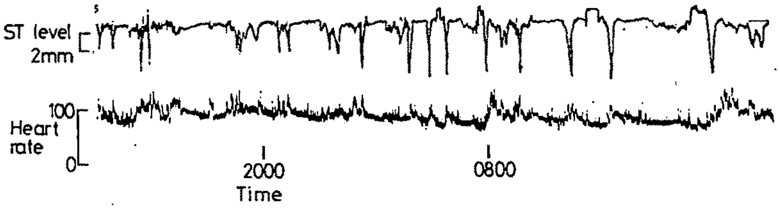


Fig. 7 *Case 3. ST elevation associated with ventricular tachycardia in the same patient. Note the very rapid return to normal. An intermittent or patient-activated recorder could have missed these changes.*

Fig. 8 Case 4. Conspicuous ST depression occurring repeatedly, and two episodes of ST segment elevation during the early morning. These two episodes are shown at a higher speed in the later part.



carpal tunnel syndrome, cervical spondylosis, a psychosomatic disorder, and peripheral neuropathy. She had undergone a full range of neurological investigations including myelograms, all of which were normal. Ambulatory monitoring showed episodes of ST depression of 1 mm or more, each of which was associated with pain in the thenar eminence. Exercise testing confirmed that the ST depression and thenar pain occurred at the peak exercise level. Coronary arteriograms showed total occlusion of the right coronary artery and 90 per cent stenosis of the circumflex artery, and ^{201}Tl scanning showed ischaemia. The patient refused operation.

Discussion

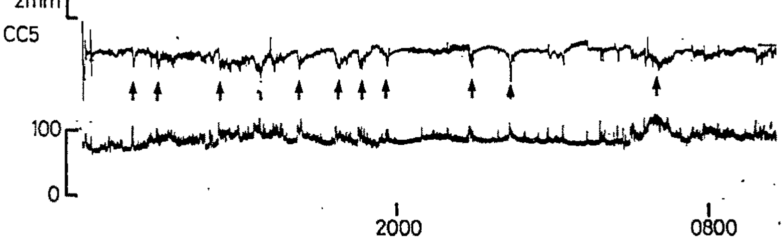
Ambulatory monitoring of the electrocardiogram to define ST segment changes is a practical and rewarding technique which can be of great diagnostic significance, particularly with regard to coronary spasm. It may also yield quantifiable data on the duration of periods of myocardial ischaemia. Early attempts to record these changes have met with justifiable criticism.[13 14] The recorders used in these studies were of the direct recording type and there were problems with phase shift and poor low frequency response. Berson and Pipberger[13] pointed out the limitations of low frequency response amplifiers and recorders and recommended the use of recorders with at least 0·05 Hz cut-off frequency. Hinkle and co-workers[14] reported the results of their tests with the Holter-Avionics system and emphasised that this should not be used for critical ST segment analysis. After improvement in the frequency response of this system, a number of studies were reported using this reel-to-reel type of recorder.[5–7]

The Oxford Medilog multichannel recorder (mark 1) is widely used in Europe. It has a claimed low frequency cut-off of 0·15 Hz but there are no validation data available on its performance characteristics. Selwyn and co-authors[9] used this system but it is doubtful if these results can be accurately quantified. The validation tests we have performed show considerable ST segment distortion, poor reproducibility of a standard 1 mV square wave, and quantitative differences from a standard reference. In contrast, the two FM recorders showed excellent reproducibility with no detectable distortion. The square wave calibrations were clean and there was no distortion of the baseline. In addition, the design of the Medilog mark 2 eliminated problems associated with recorder-cable junction movement and the calibration remained stable over a 24 hour period.

Even though the programmed recorder (Cardiocassette) could be used to sample ST changes every 15 minutes or during symptoms, we found instances when its use would have missed significant events. For example, in case 3 there was transient ST elevation which disappeared within a minute (Fig. 6 and 7). Furthermore, there were at least six episodes of ST depression in case 5 which occurred at night while the patient was asleep and which were painless. It appears that if realtime recorders are to be used a sampling rate of at least once a minute would be necessary.

Our investigation clearly showed the need for careful attention to the electrode system whatever the quality of the tape recorder. We devoted

Fig. 9 Case 5. ST segment depression occurring during exertional pain (↑) in the left thenar eminence and during the night also.



considerable time and effort to improve signal quality. It was found to be absolutely essential to shave the hair, clean the skin with isopropyl alcohol, abrade the skin with a high speed dental rotary burr, and use stable electrodes. The application of four electrodes took seven to 10 minutes and the time and care spent on this was always worth while. Fixing the electrodes with a porous elastic bandage (Coban) was satisfactory. However, this occasionally produced skin irritation and specially designed elasticated vests were found to be more satisfactory.

One of the disadvantages of ambulatory monitoring is the generation of large amounts of data which require automated methods for its analysis. We have used an ST segment trend system using two spots, one located on the PR segment and the other at the J-point. This system excludes artefacts and ectopic beats automatically. Our validation data were obtained by converting the signals into real time and analysing them with the CASE system; this could be done as the recordings lasted only 20 to 30 minutes each. This method is clearly impracticable for routine use and we are now exploring the possibility of developing a purpose built programable minicomputer for ST segment analysis in accelerated time.

The detection of at least two episodes of painless ST segment change for every painful episode is of importance both prognostically and therapeutically. Furthermore, the successive occurrence of ST depression and ST elevation suggests coronary artery spasm even in ambulant subjects with relatively stable angina; this interpretation is supported by the recording of such changes at night with little or no tachycardia. Accurate and reliable ambulatory FM recording of the ST segment for 24 hours or more appears to be a valuable method of examining the profile of changes in ischaemic heart disease. It does not render exercise testing superfluous, as it yields different and useful additional information.

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References

1 Harrison DC, Fitzgerald JM, Winkle RA. Ambulatory electrocardiography for diagnosis and treatment of cardiac arrhythmias. *N Engl J Med* 1976; **294:** 373–80.

2 Raftery EB, Cashman PMM. Long term recording of the electrocardiogram in a normal population. *Postgrad Med J* 1976; **52,** suppl 7: 32–8.

3 Kennedy HL, Caralis DG. Ambulatory electrocardiography—a clinical perspective. *Ann Intern Med* 1977; **87:** 729–39.

4 Gillilan RE, Babitt HI, Warbasse JR. Clinical accuracy of ECG ischaemic ST segment changes by electromagnetic tape and by radiotelemetry. *Circulation* 1970; **42,** suppl III: 157.

5 Stern S, Tzivoni D. The reliability of Holter-Avionics system in reproducing the ST segment (letter). *Am Heart J* 1970; **84:** 427–8.

6 Stern S, Tzivoni D. Early detection of silent ischaemic heart disease by 24 hour electrocardiographic monitoring of active subjects. *Br Heart J* 1974; **36:** 481–6.

7 Wolf E, Tzivoni D, Stern S. Comparison of exercise test and 24 hour ambulatory electrocardiographic monitoring in detection of ST-T changes. *Br Heart J* 1974; **36:** 90–5.

8 Allen RD, Gettes LS, Phalan C, Avington D. Painless ST segment depression in patients with angina pectoris. *Chest* 1976; **69:** 467–73.

9 Selwyn AP, Fox K, Eves M, Oakley D, Dargie H, Shillingford J. Myocardial ischaemia in patients with frequent angina pectoris. *Br Med J* 1978; **ii:** 1594–6.

10 Balasubramanian V, Raftery EB, Stott FD. Myocardial ischaemia in patients with frequent angina pectoris (letter). *Br Med J* 1979; **i:** 198.

11 American Heart Association Committee on Electrocardiography. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. *Circulation* 1975; **52** (2): 11–31.

12 Bonoris PE, Greenberg PS, Christison GW, Castellanet MD, Ellestad MH. Evaluation of R wave amplitude changes versus ST segment depression in stress testing. *Circulation* 1978; **57:** 904–10.

13 Berson AS, Pipberger HV. The low frequency response of electrocardiographs, a frequent souce of recording errors. *Am Heart J* 1966; **71:** 779–89.

14 Hinkle LE Jr, Meyers J, Stevens M, Carver S. Tape recordings of the ECG of active men. Limitations and advantages of the Holter-Avionics instruments. *Circulation* 1967; **36:** 752–65.

Requests for reprints to Dr E B Raftery, Northwick Park Hospital and Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ.

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Electrocardiographic characteristics of neurocirculatory asthenia during everyday activities

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SUMMARY We describe the electrocardiographic changes during everyday activities recorded by ambulatory electrocardiographic monitoring in 67 patients with neurocirculatory asthenia. The findings were compared with the results of ambulatory monitoring in 33 healthy controls. We observed episodes of sinus tachycardia >120/min unrelated to effort in 60 of the patients, 35 had frequent episodes of pronounced sinus arrhythmia, 16 showed transient ST depression, and six transient ST elevation. All these changes appeared during the patients' routine activities, without any unusual exertion and frequently at rest. Periods of sinus tachycardia and sinus arrhythmia were recorded from the patients during sleep. Cardiac arrhythmias, especially ventricular premature beats, were also much more common in those with neurocirculatory asthenia than in the control subjects. These findings indicate that ambulatory electrocardiographic monitoring provides important information on the electrocardiographic characteristics of patients with neurocirculatory asthenia and helps to establish this diagnosis in obscure cases.

Neurocirculatory asthenia is a multisystemic disease involving the cardiovascular, nervous, and respiratory systems described by Da Costa[1] as "the irritable heart of the soldiers" during the American Civil War. Since then, it has been detected in soldiers and other young adults in several countries[2 3] and called "soldier's heart", "effort syndrome",[3] or "Da Costa's syndrome",[4] but recently the name neurocirculatory asthenia has become the most popular. The most prominent manifestation of this syndrome is palpitation, but many patients also suffer from praecordial pains, anxiety, dyspnoea, fatigue, and other non-specific complaints. Among civilians, it is twice as common in women as in men.[5] The onset of the symptoms is usually between the ages of 20 and 30. The haemodynamic features of the disease are high cardiac output, reduced peripheral flow,[6] and sinus tachycardia, both at rest and in an erect position. These features tend to be exaggerated during effort.[5 7] Frequently, fluctuations in blood pressure are pronounced.[8] The patient's physical condition is often poor; this can be improved by exercise.[9 10] In many of the patients ST-T changes in the electrocardiogram are evoked by a change of position[11] or by effort testing.[8] Therefore many of them are erroneously diagnosed as suffering from organic heart disease, for example myocardial ischaemia or myocarditis.

In spite of the above quoted studies, no strict criteria for the diagnosis of neurocirculatory asthenia have been established as yet. The existence of a rapid resting heart rate during casual examination during the day is a generally accepted feature on which this diagnosis is based.[4] There are, however, no reliable data on the behaviour of heart rate and other electrocardiographic features in such subjects under "physiological" conditions during everyday activities, emotional stress, or sleep. In this study we describe the heart rate, rhythm, and ST-T changes in patients with neurocirculatory asthenia during their daily activities, recorded by ambulatory electrocardiographic monitoring.

Patients and methods

In this study we included 67 patients aged 18 to 35 years (mean 27) in whom the diagnosis of neurocirculatory asthenia was established clinically. The diagnosis was based upon the usually accepted definitions and characteristics of somatic symptoms.[12] In our patients, palpitation was experienced by 45 patients, chest pain by 17 patients, hyperventilation and dyspnoea by 27 patients, anxiety by 26 patients, and vague praecordial

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symptoms and dull pressure by 32 patients. The complaints are detailed in Table 1. Physical examination and chest *x*-rays in all patients revealed no signs of organic heart or lung disease. Routine resting electrocardiograms showed sinus tachycardia above 100/min in 17 patients, ST depression of the "junctional" type in six patients, and flat or inverted T waves in 10 patients. No ectopic activity was detected in the routine electrocardiograms. Thyrotoxicosis, mitral valve prolapse, hypertrophic subaortic stenosis, and anaemia were excluded.

A group of 33 individuals served as a control group. They comprised 22 men and 11 women with ages ranging from 24 to 34 years (mean 29). All volunteered for the test after being examined by one of our team at the gynaecology or gastroenterology outpatient clinics. None of them suffered from any cardiovascular symptoms and physical examination and electrocardiograms did not disclose any cardiac or lung abnormalities. All of them were employed but not in medical or paramedical work; they performed their usual daily activities during the day of the monitoring. The length of sleep was the usual average for people of similar age.

Ambulatory electrocardiographic monitoring was performed from one morning to the next both in the group of patients and in the controls. The examinees were requested to follow their usual daily routine, and to keep a meticulous diary of all activities and possible symptoms. These were subsequently related to the electrocardiographic findings. The mode of operating the ambulatory electrocardiographic monitoring system, the positioning of the electrodes, and the technique of interpretation have been detailed in previous reports.[13–15] The Avionics system used in this study was checked for its low-frequency response which fulfilled the American Heart Association (AHA) requirements and recorded satisfactorily the ST-T segment. The magnetic tapes were scanned visually by a trained technician both for arrhythmias and ST-T alterations and the final interpretation was always confirmed by a physician.

Table 1 *Complaints of patients with neurocirculatory asthenia*

Complaints	*No. of patients*
Palpitation	45
Praecordial symptoms	32
Fatigue	28
Dyspnoea	27
Anxiety	26
Praecordial pain	17
Dizziness	11
Other (sweating, headaches, etc.)	12

Table 2 *Electrocardiographic findings on monitoring in patients with neurocirculatory asthenia and in control group*

		NCA (67 patients)	*Control (33 subjects)*
Episodes of sinus tachycardia without physical effort	> 150/min	23	—
	> 120/min	60	4
	> 100/min	67	8
Episodes of sinus bradycardia	< 35/min	14	1
Episodes of sinus tachycardia during sleep	> 90/min	30	3
Episodes of sinus arrhythmia		35	4

As in all our other investigations dealing with ambulatory electrocardiographic monitoring, control electrocardiograms were recorded in the supine and erect positions and during hyperventilation. These would reveal any changes caused by posture or respiration.

Results

HEART RATE

The most consistent finding in patients with neurocirculatory asthenia was the tendency towards sinus tachycardia (Table 2). In 23 of the patients frequent episodes of a heart rate of above 150/min were documented during their daily routine, apparently without undue physical effort. None of the control subjects reached such a heart rate during daily activities. In 60 of the 67 patients, periods with a heart rate of above 120/min occurred repeatedly, and all 67 had episodes of sinus tachycardia faster than 100/min during the day of monitoring. In the control subjects only four attained a heart rate above 120/min, while eight reached heart rates of more than 100/min without undue effort. During undisturbed sleep at night, periods of sinus tachycardia between 90 and 120/min were observed in 30 patients with neurocirculatory asthenia and in only three subjects in the control group.

Sinus arrhythmia, defined as variations in cycle length exceeding the upper limit of 120 ms between the longest and shortest cardiac cycles,[16] was documented during usual daily activities in 35 of the patients. Up to 20 episodes each day of the nonphasic (nonrespiratory) form[16] were observed. The undue acceleration of the pulse was usually unconnected with change of posture or physical effort. In 20 of the patients the sinus arrhythmia was even more obvious during sleep. In the control

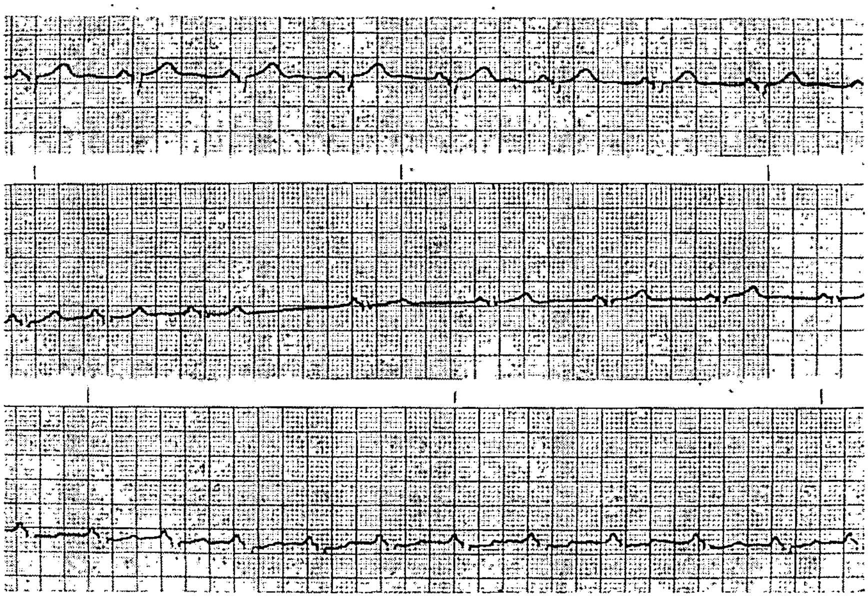

Fig. 1 *Variations in sinus rate in a patient with neurocirculatory asthenia recorded during a 24 hour period.* Upper panel: *normal sinus rhythm.* Middle panel: *pronounced sinus arrhythmia.* Lower panel: *sinus tachycardia at rest.*

group only four subjects showed such sinus arrhythmia during the monitoring period. Representative electrocardiograms are illustrated in Fig. 1.

RHYTHM DISTURBANCES

Disturbances in cardiac rhythm were observed more frequently in patients with neurocirculatory asthenia than in control subjects (Table 3). Ventricular premature beats were detected in 12 patients but in only three control subjects. One patient with neurocirculatory asthenia also had a short bout of ventricular tachycardia (Fig. 2). Ectopic atrial activity was found in five patients and one patient had transient nodal rhythm.

ST-T SEGMENT ALTERATIONS

Forty-six of the 67 patients with neurocirculatory asthenia had ST-T changes during the monitoring period. The types of the ST-T changes are detailed in Table 4. The most common findings were flattening or inversion of the T wave (Fig. 3). ST segment depression of the "junctional" or J point type (Fig. 4) was found in 12 patients. Segmental downsloping or horizontal ST depression 0·5 to 1·0 mm, using the PR segment as the baseline reference (Fig. 3), was found in four patients. All four patients underwent thallium-201 stress testing which was normal in all, indicating absence of coronary artery disease. Both types of ST changes occurred only when the heart rate was above 110/min. In the controls, the "junctional" type of ST depression was seen in three subjects, but the "segmental" type in none. ST elevation of 1 mm or more, lasting for at least 12 seconds (observed during a period when the electrocardiograph recording had a stable isoelectric line and the QRS

Table 3 *Arrhythmias found in 67 patients with neurocirculatory asthenia and 33 control subjects*

	VPB's > 5/min	*VPB's 5–2/min*	*VPB's ≤1/min*	*APB's > 5/min*	*APB's 5–2/min*	*APB's ≤1/min*	*APB's coupled*	*APB's blocked*	*Transient nodal rhythm*
Neurocirculatory asthenia	2	4	6	1	1	1	1	1	1
Control	1	1	1	—	—	1	—	—	—

VPB, ventricular premature beat; APB, atrial premature beat.
The figures concerning the frequency of ectopic beats relate to the most frequent ectopic activity observed during the 24 hour monitoring period.

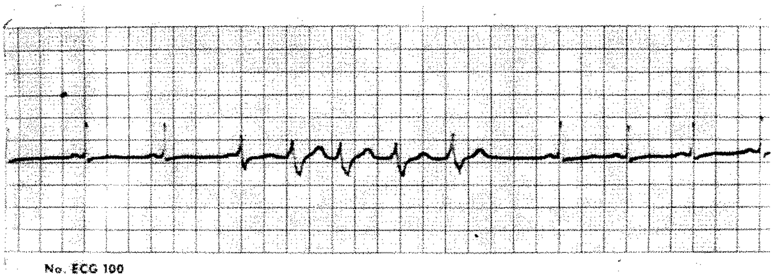

Fig. 2 *Short bout of ventricular tachycardia in a 34-year-old patient with neurocirculatory asthenia.*

complexes were identical with those preceding the ST elevation), was seen in six patients with neurocirculatory asthenia and in none of the control subjects; in three of the patients the ST elevation occurred during undisturbed sleep (Fig. 5).

Discussion

Neurocirculatory asthenia is a disease of young adults, featured by distressing symptoms such as palpitation and chest pain. Because of the variety of the symptoms, the syndrome is not easily diagnosed. With the use of the 24-hour ambulatory electrocardiographic monitoring technique we examined a series of 67 patients in their normal environment and during their usual routine activities. We demonstrated that the tendency towards sinus tachycardia in neurocirculatory asthenia prevails not only during physical effort, but is present also during quiet activity and even during rest. These episodes of sinus tachycardia unprovoked by physical effort seem to us to be the characteristic feature of neurocirculatory asthenia, related probably to the beta-adrenergic over-

Table 4 *ST-T changes found in 67 patients with neurocirculatory asthenia and 33 control subjects*

ST-T changes	*No. of NCA patients*	*No. of control subjects*
ST depression	16	3
segmental (horizontal or downsloping)	4	—
junctional ("J point")	12	3
Flat T	25	4
Biphasic T	3	1
Inverted T	27	5
ST elevation	6	—

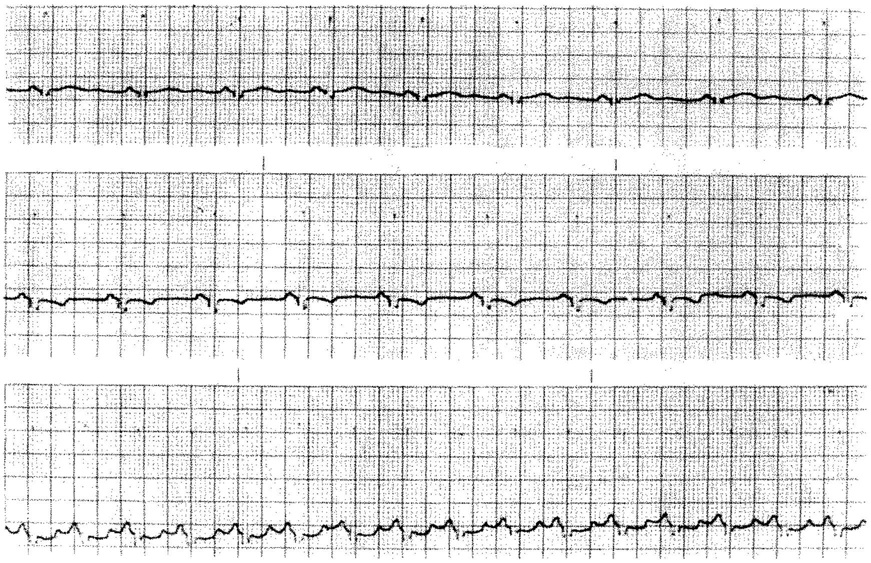

Fig. 3 *Variations in ST and T waves in a patient with neurocirculatory asthenia.* Upper panel: *electrocardiogram during most of the day.* Middle panel: *inversion of T wave at rest.* Lower panel: *segmental ST depression during driving associated with sinus tachycardia.*

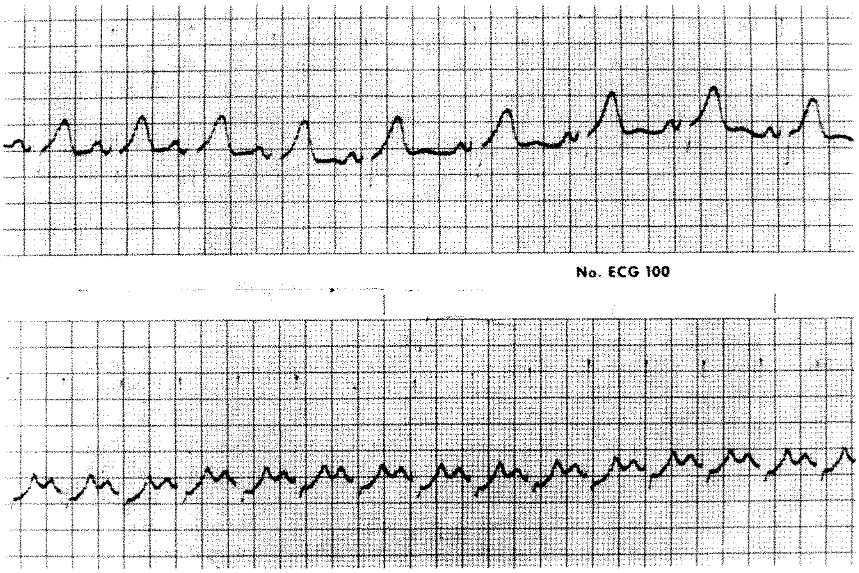

Fig. 4 *Junctional type of ST depression in a patient with neurocirculatory asthenia.* Lower panel: *recorded while walking; normal electrocardiogram during most of the day* (upper panel).

activity existing in this syndrome.[17] In contrast to our findings, Cohen and White[18] found only a few abnormalities under basal and rest conditions, and claimed that the anomalies occurred mainly in response to a variety of stresses. This difference may be related to the fact that the important contribution of Cohen and White to the subject of neurocirculatory asthenia in the 1950s was based on findings in routine electrocardiograms, a method which did not enable the episodic and transient changes prevailing in this syndrome to be detected

Although a "great lability of the pulse" has been mentioned by Wood[4] as a possible feature of Da Costa's syndrome, the presence of sinus arrhythmia has not yet been properly stressed in published reports dealing with neurocirculatory asthenia. The frequency of sinus arrhythmia documented in more than half of our patients emphasises that this may be an important diagnostic feature of the syndrome.

The behaviour of the heart rate during sleep has

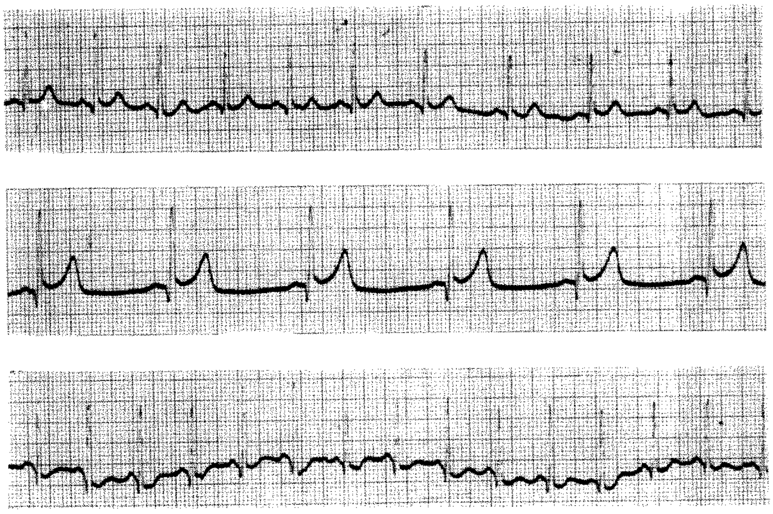

Fig. 5 *Ambulatory electrocardiographic monitoring in a 28-year-old woman, showing sinus arrhythmia at rest* (upper panel); *sinus bradycardia during sleep, associated with ST elevation* (middle panel); *sinus tachycardia during walking, accompanied by slight ST depression and flattening of T wave* (lower panel).

not previously been investigated in patients with neurocirculatory asthenia. Our patients showed a tendency towards episodes of rapid heart rate during sleep as well as during the day. In 30 of the patients periods with a heart rate above 90/min during undisturbed sleep were observed, accompanied by pronounced sinus arrhythmia and bradycardia. We do not know whether these nocturnal alterations occurred during dreaming periods or changes in body position during sleep. We assume that these changes are an expression of the sympathetic overactivity prevailing also during sleep.

Changes in the ST segment and/or T wave are frequently described in patients with neurocirculatory asthenia during provocation tests and sometimes even at rest.[8 11] In this study we showed that in most patients these alterations appear during quiet activity, without effort or provocation. They seem to be of the so-called "non-specific" type, namely flattening and inversion of T waves, and "junctional" ST depression. "Horizontal" ST depression occurred only in association with sinus tachycardia. The four patients with this feature also had the other characteristics of neurocirculatory asthenia, that is frequent episodes of resting tachycardia and sinus arrhythmia. A normal thallium-201 stress test ruled out coronary disease in all four. Holmgren *et al.*[8] also found occasional ST abnormalities in patients with neurocirculatory asthenia. A striking finding in our study was the demonstration of periods of ST segment elevation on monitoring in six of the 67 patients. Transient ST segment elevation has been described previously in normal young subjects, especially in blacks,[19] and was attributed to autonomic imbalance. In a previous study[20] of 174 patients evaluated by ambulatory electrocardiographic monitoring for chest pain and/or palpitation, only seven had ST elevation, two of whom were diagnosed as neurocirculatory asthenia. None of our young control subjects demonstrated this finding. ST elevation may be one of the electrocardiographic characteristics of neurocirculatory asthenia which will be detected more often if 24 hour monitoring is used more frequently for these patients.

Exercise testing is a useful method for evaluation of patients with neurocirculatory asthenia. The excessive tachycardia response to effort, the occasional occurrence of ST-T changes during the period of tachycardia, and the frequently reduced physical capacity, are demonstrable by effort testing.[8 11] Ambulatory electrocardiographic monitoring is capable of detecting these changes and can, in addition, provide data on the behaviour of the heart rate and other electrocardiographic indices unrelated to physical effort. In our opinion, tachycardia during rest is more characteristic of neurocirculatory asthenia than is exercise-induced rapid heart rate, and is more frequently related to patients' symptoms. The relation between the symptoms and the episodes of tachycardia can be demonstrated convincingly by ambulatory electrocardiographic monitoring.

We conclude that ambulatory electrocardiographic monitoring is a useful method for assessing patients known or suspected to have neurocirculatory asthenia. Sinus tachycardia at rest during the day and during sleep, an exaggerated tachycardiac response to physical effort, frequent episodes of severe sinus arrthymia, ST-T changes, and characteristic symptoms all contribute to the correct diagnosis of this syndrome.

References

1 Da Costa JM. *Medical diagnosis.* Philadelphia: JB Lippincott, 1864.

2 Myers ABR. On the aetiology and prevalence of diseases of the heart among soldiers. London: J Churchill, 1870.

3 Lewis T. Report upon soldiers returned as cases of "disordered action of the heart" (D.A.H.) or "valvular disease of the heart" (V.D.H.). *Spec Rep Ser Med Res Comm* 1917; **8.**

4 Wood P. Da Costa's syndrome (or effort syndrome). *Br Med J* 1941; **i:** 767–72, 805–11, & 845–51.

5 Cohen ME, White PD. Neurocirculatory asthenia: 1972 concept. *Milit Med* 1972; **137:** 142–4.

6 Juchems RH. Circulation times in patients with neurocirculatory asthenia. *Am Heart J* 1964; **67:** 583–7.

7 Holmgren A, Jonsson B, Levander M, Linderholm H, Sjöstrand T, Ström G. Low physical working capacity in suspected heart cases due to inadequate adjustment of peripheral blood flow (vasoregulatory asthenia). *Acta Med Scand* 1957; **158:** 413–36.

8 Holmgren A, Jonsson B, Levander M, Linderholm H, Sjöstrand T, Ström G. ECG changes in vasoregulatory asthenia and the effect of physical training. *Acta Med Scand* 1959; **165:** 259–71.

9 Holmgren A, Jonsson B, Levander M, *et al.* Physical training of patients with vasoregulatory asthenia. *Acta Med Scand* 1957; **158:** 437–46.

10 Holmgren A, Jonsson B, Levander M, *et al.* Effect of physical training in vasoregulatory asthenia, in Da Costa's syndrome, and in neurosis without heart symptoms. *Acta Med Scand* 1959; **165:** 89–103.

11 Mann A, Wintner I, Kellerman JJ. The orthostatic test in neurocirculatory asthenia (Hebrew). *Harefuah* 1973; **84:** 428.

12 Hurst JW, Logne R, Schlant RC, Wenger NK. *The heart, arteries and veins.* 3rd ed. New York: McGraw-Hill, 1978: 1805–9.

13 Wolf E, Tzivoni D, Stern S. Comparison of exercise tests and 24-hour ambulatory electrocardiographic

monitoring in the detection of ST-T changes. *Br Heart J* 1974; **36:** 90–5.

14 Stern S, Tzivoni D. Early detection of silent ischaemic heart disease by 24-hour electrocardiographic monitoring of active subjects. *Br Heart J* 1974; **36:** 481–6.

15 Stern S, Tzivoni D, Stern Z. Diagnostic accuracy of ambulatory ECG monitoring in ischemic heart disease. *Circulation* 1975; **52:** 1045–9.

16 Hurst JW, Logne R, Schlant RC, Wenger NK. *The heart, arteries and veins.* 3rd ed. New York: McGraw-Hill, 1978: 644.

17 Frohlich ED. Beta adrenergic blockade in the circulatory regulation of hyperkinetic states. *Am J Cardiol* 1971; **27:** 195–9.

18 Cohen ME, White PD. Life situations, emotions and neurocirculatory asthenia (anxiety neurosis, effort syndrome). *Psychosom Med* 1951; **13:** 335–57.

19 Wasserburger RH, Lorenz TH. The effect of hyperventilation and probantine on isolated RS-T segment and T-wave abnormalities. *Am Heart J* 1956; **51:** 666–83.

20 Golding B, Wolf E, Tzivoni D, Stern S. Transient S-T elevation detected by 24-hour ECG monitoring during normal daily activity. *Am Heart J* 1973; **86:** 501–7.

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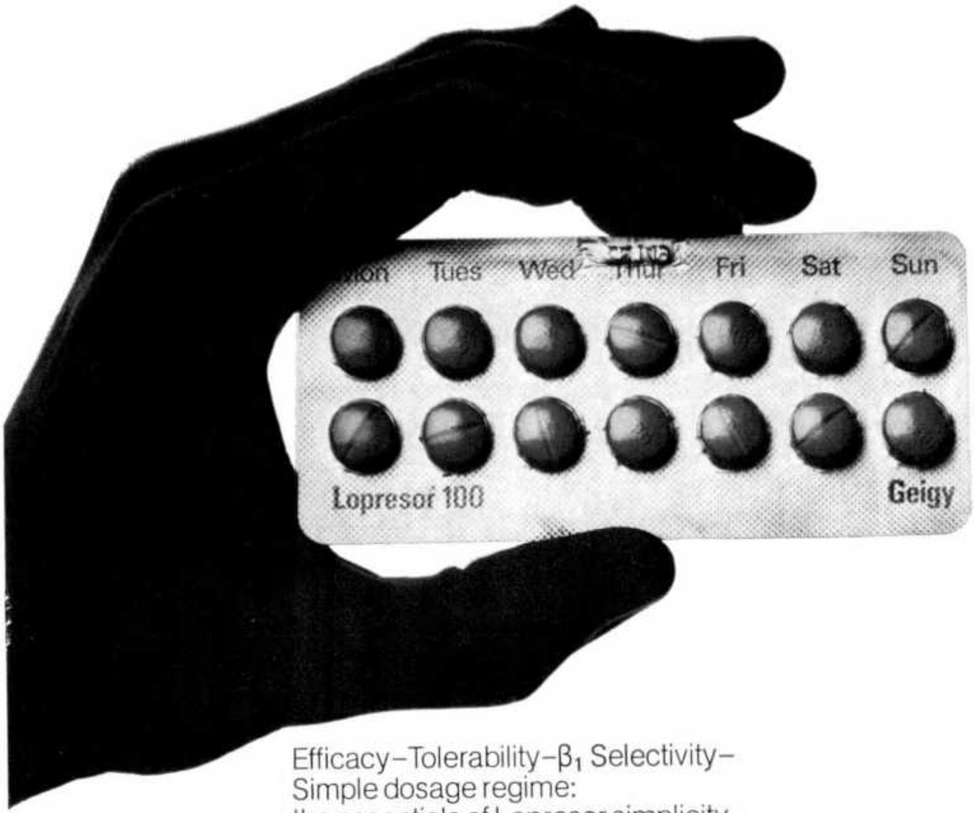

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Br Heart J 1980; **44:** 433–43

Histopathological specificity of hypertrophic obstructive cardiomyopathy

*Myocardial fibre disarray and myocardial fibrosis**

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SUMMARY The topography and specificity of fibre disarray and fibrosis in hypertrophic obstructive cardiomyopathy were determined in a histological study comprising 40 necropsy hearts—10 with hypertrophic cardiomyopathy, 10 with congestive cardiomyopathy, 10 with aortic valve stenosis, and 10 normal hearts. Seven standard regional sections were sampled from each heart and graded "double-blind" (tissue location and disease entity) for severity and extent of fibre disarray and four distinct types of myocardial fibrosis. Statistical comparison of the severity and distribution of indices of fibre disarray and fibrosis within each group and between the normal and the disease groups showed that fibre disarray and fibrosis were qualitatively non-specific for hypertrophic cardiomyopathy. However, when fibre disarray was quantified (1) it was significantly increased in hypertrophic cardiomyopathy and allowed separation of hearts with hypertrophic cardiomyopathy from normal hearts and from those with congestive cardiomyopathy and aortic stenosis, (2) it did not vary significantly among sections of the left ventricle (that is, between the septum and the free wall) in hypertrophic cardiomyopathy, (3) it was closely associated with plexiform fibrosis, and (4) it varied independently of wall and septal thickness. Though the histogenesis of fibre disarray is unknown, it probably represents an exaggeration of a non-specific common pathway for many diverse pathophysiological processes.

Since the early descriptions of hypertrophic obstructive cardiomyopathy by Teare[1] and Brock,[2] this clinical disorder has been diagnosed at the bedside by the presence of a sharp carotid upstroke, a high-frequency systolic murmur, and a hyperdynamic apical impulse[3–5]; at cardiac catheterisation by the presence of a left ventricular outflow tract gradient at rest or on provocation[3–7]; on the echocardiogram by the presence of asymmetric septal hypertrophy[8–10] and systolic anterior motion of the mitral valve[11]; and pathologically by the myocardial fibre disarray and fibrosis in the disproportionately thickened interventricular septum.[1 12–15]

Recently, the specificity of echocardiographic features of hypertrophic cardiomyopathy has been seriously questioned.[16 17] Similarly, septal fibre disarray, initially thought to be pathognomonic of hypertrophic cardiomyopathy,[1 13 14] has been found to be present in normal hearts,[18 19] in many congenital malformations—particularly those in which the pattern of contraction is abnormal[20]—and also in animals after chronic endocardial pacing.[21]

Hitherto, there has been no systematic attempt to quantify the severity and distribution of fibre disarray and fibrosis in the transverse and longitudinal axes of the right and left ventricles in hypertrophic cardiomyopathy. We undertook such an evaluation (1) to investigate the specificity of fibre disarray as a histological marker in hyper-

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Table 1 *Sex, age, and heart weights in four groups: Normal, hypertrophic (obstructive) cardiomyopathy (HOCM), congestive cardiomyopathy (COCM), and aortic stenosis (AS)*

Group	*No. of hearts*	*Sex*		*Age, mean (range) (y)*	*Heart weight (g)*
		F	*M*		
Normal	10	6	4	43·3 (21–54)	324 (280–380)
HOCM	10	5	5	48·4 (14–72)	587 (300–830)
COCM	10	3	7	50·6 (40–81)	548 (400–760)
AS	10	3	7	71·5 (28–89)	532 (300–770)

trophic cardiomyopathy, (2) to determine whether there was a relation between fibre disarray and fibrosis and left ventricular hypertrophy, and (3) to study whether variation in the severity and distribution of fibre disarray and fibrosis might account for the variation in left ventricular function demonstrable both echocardiographically[22 23] and angiocardiographically.[24]

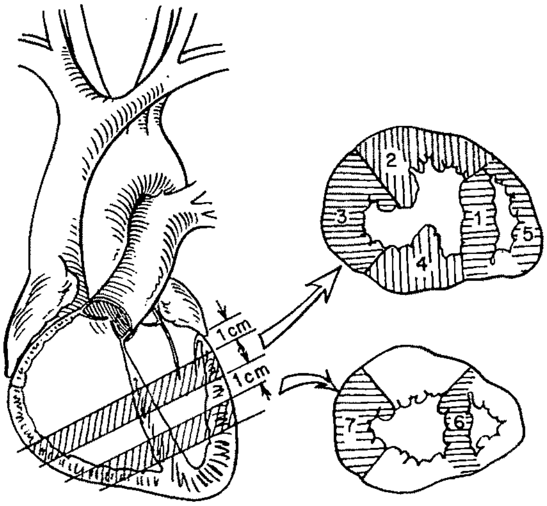

Fig. 1 *Two complete transverse segments were taken from each heart 1 cm and 3 cm below mitral valve annulus. Complete left and right ventricular walls and septum were represented in upper segment, and septum and lateral left ventricular wall in lower segment. Tissue blocks for histological study were taken from section locations 1 to 7. Section 1, upper septum; 2, anterior left ventricular wall; 3, upper lateral left ventricular wall; 4, posterior left ventricular wall; 5, right ventricular wall; 6, lower septum; and 7, lower lateral left ventricular wall.*

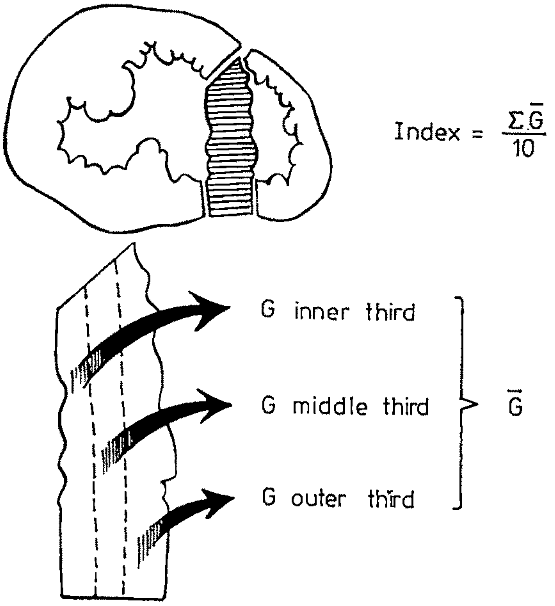

Fig. 2 *Tissue sections were divided into three regions, inner third, middle third, and outer third, with reference to left ventricular endocardial surface. Fibre disarray and each type of fibrosis were graded for each third* (G). *Score for section as a whole was expressed as a mean of three regions* ($\overline{G}$). *Numerical index for fibre disarray and each type of fibrosis was then obtained for each section locations 1 to 7 (Fig. 1) within each group (1 to 4) by dividing sum of mean grade of each section* ($\Sigma\overline{G}_1, \overline{G}_2 \ldots \overline{G}_{10}$) *by number of patients in each group (10).*

Materials and methods

A total of 40 necropsy hearts was studied. They comprised the following four groups, in none of which was there coronary artery stenosis with greater than 75 per cent cross-sectional luminal narrowing.

Group 1 consisted of 10 "normal" hearts from patients 21 to 54 years of age (mean 43 years) who had died from noncardiac causes. Group 2 consisted of 10 hearts from patients 14 to 72 years of age (mean 48 years) who had had a clinical diagnosis of hypertrophic cardiomyopathy and the concordant necropsy findings described by Davies *et al.*[25] and Roberts and Ferrans.[26] Group 3 consisted of 10 hearts from patients 40 to 81 years of age (mean 51 years) who had had idiopathic congestive cardiomyopathy with severely dilated ventricles. Group 4 consisted of 10 hearts from patients 28 to 89 years of age (mean 72 years) who had critical calcific aortic valve stenosis and severe left ventricular hypertrophy with similar heart weights and wall thickness as the hearts with hypertrophic cardiomyopathy (Table 1).

The mean ages and sex distribution of the normal patients and those with hypertrophic and congestive cardiomyopathy (groups 1 to 3) were similar, but the mean age in patients with aortic stenosis (group 4) was greater; this difference reflects the different natural history of aortic stenosis. The means and ranges of the heart weights in the three disease groups (groups 2 to 4) were similar, and they were significantly greater ($p < 0{\cdot}01$) than those in the normal patients (group 1) (Table 1).

Tissue blocks for histological study were taken from each heart at two levels 1 cm and 3 cm below the mitral valve annulus (Fig. 1). The complete left and right ventricular walls and the septum were represented in the upper level, and the septum and the lateral left ventricular wall at the lower level (Fig. 1). Consecutive paraffin-embedded 5 μm tissue sections were stained with haematoxylin and eosin, elastic van Gieson, and Mallory-Heidenhain connective tissue stains. Each tissue section in locations 1 to 7 (Fig. 1) from the 40 hearts was assigned a random nonconsecutive number so that the two pathologists evaluating the severity of fibre disarray and fibrosis had no knowledge of the location of the tissue sample or of the group from which the tissue was obtained.

Tissue from each section location was divided into three regions—the inner third, middle third, and outer third, with reference to the left ventricular endocardial surface (Fig. 2). Fibre disarray and fibrosis were graded for each third, and the score for the section as a whole was expressed as a mean of three regions (Fig. 2).

Histologically, the presence or absence of fibre disarray in any given histological section was graded in ascending order of severity from 0 to 4 (Fig. 3). In grade 0 fibre disarray was not present. Grade 1 was assigned when 75 per cent or more of the area of the section showed muscle fibres characterised by normal side-branching fibres and parallel fibres in approximately equal proportions; in grade 2, side-branching muscle fibres were of approximately equal number to parallel fibres but occurred at a more obtuse angle than normal; in grade 3, in 50 to 75 per cent of the area of the section the apparent unidirectional nature of the myocardial fibres was lost because of formation of multiple orthogonal branches and incomplete whorls; and in grade 4, there was severe disruption of the normal orderly alignment of myocardial fibres, with complete and complex whorl formation.

Fibrosis was divided into four distinct types as follows (Fig. 4): (1) the term "microscopical scars" was used to describe foci of replacement fibrosis not discernible to the naked eye; (2) "interstitial fibrosis" refers to strands or bundles of collagenous connective tissue encircling or surrounding the individual myocardial fibres; (3) "perivascular fibrosis" refers to the condensation of collagenous connective tissue around intramural blood vessels, blending with the adventitia; and (4) "plexiform fibrosis" refers to a unique type of interstitial fibrosis seen in foci of myocardial fibre disarray in which fine and coarse bands of collagen, often with a wavy, "crimped" appearance, interlaced or enveloped the myocardial fibres.[27]

The severity of each histological type of myocardial fibrosis was also graded from 0 to 4 in ascending order of severity, in which grade 0 indicated not present. In addition, the transmural thickness (endocardial to endocardial, or endocardial to epicardial surface) of the tissue sections

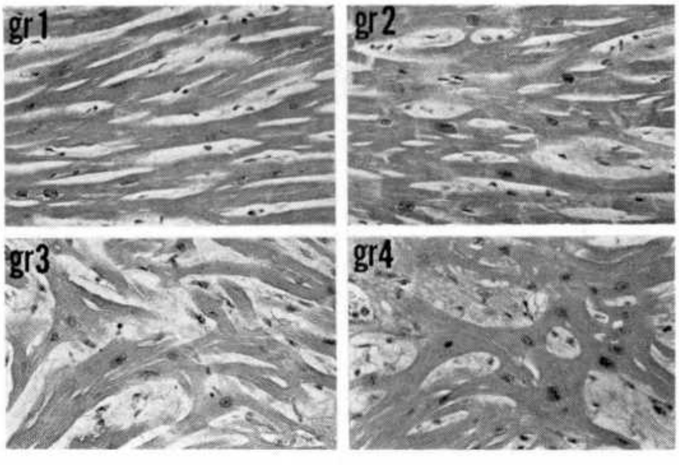

Fig. 3 *Histological grades (gr) of myocardial fibre disarray in ascending order of severity; grades 1 and 2 are normal variations but 3 and 4 represent true fibre disarray. (Haematoxylin and eosin. ×480.)*

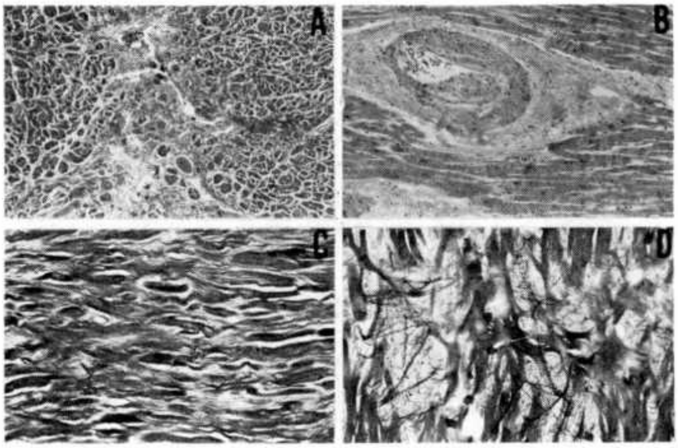

Fig. 4 *Representative photomicrographs of four histologically distinct types of myocardial fibrosis.*
A, *microscopical scars;*
B, *perivascular fibrosis;*
C, *interstitial fibrosis; and*
D, *plexiform fibrosis. (Mallory-Heidenhain. × 160.)*

was measured for each section location (1 to 7), and this was used as quantification of free wall and septal thickness, that is ventricular hypertrophy (Table 2).

When the grading of fibre disarray and individual types of fibrosis and the measurement of wall thickness of all sections had been completed, the observer double-blind (tissue location and disease entity) study code was broken and the histological slides were separated into the disease entity groups (four) and tissue-section locations (seven). A numerical index for fibre disarray and for each type of fibrosis was then obtained for each section location in each group by dividing the sum of the mean grade of each section by the number of patients in each group[9] (Fig. 2).

With the use of these indices of fibre disarray and fibrosis at each section location, not only was the severity of these factors assessed but the distribution of each was also evaluated throughout the transverse and longitudinal axes of the heart within each disease group. Subsequently, the severity and distribution of fibre disarray and fibrosis in aortic stenosis and hypertrophic and congestive cardiomyopathy were compared with normal and with one another. In addition, we investigated the relation between fibre disarray index, each type of fibrosis index, and wall thickness in the four groups.

Numerical data for each variable in all section locations 1 to 7 (Fig. 1) are given in Tables 2 to 7. (*Note:* in Fig. 5 and 7 to 10, for the purposes of clarity and simplicity, only sections 1 to 4 are shown, that is, all sections from the tissue slice taken 1 cm below the mitral annulus, because indices of fibre disarray and fibrosis from sections 6 and 7, taken from 3 cm below the mitral annulus, were not significantly different from those of sections 1 to 4 in each disease group and in the normal group.)

Statistical methods

For each diagnostic group and each index listed above, formal tests of significance were used to determine whether differences existed among sections of the heart. These tests, based on Hotelling's T^2,[28] are "overall" tests that considered all sections simultaneously. In general, such overall tests were followed by further paired comparisons of subgroups only when a statistically significant ($p < 0{\cdot}05$) result was obtained.

In the absence of evidence of section differences for any of the indices, each index was summed over the six sections constituting the left ventricle for comparisons among diagnostic groups. Such comparisons, carried out separately for left and right ventricles, were based on one-way analysis of variance. This is an overall test that considered the four groups simultaneously. Paired comparisons were made only when the analysis of variance

Table 2 *Wall thickness for section locations 1 to 7 in the four groups studied**

Group	*No. of hearts*	*Left ventricular wall thickness (mm) for each section location (Fig. 1) (Mean and SE)*						*Right ventricular wall thickness (mm)*
		1	*2*	*3*	*4*	*6*	*7*	*5*
Normal	10	12·2 ±1·2	12·1 ±1·0	14·0 ±0·8	13·6 ±0·9	13·0 ±1·2	15·1 ±1·5	5·6 ±0·4
HOCM	10	20·6 ±1·9	20·4 ±2·2	20·8 ±1·5	17·5 ±1·3	22·5 ±1·8	19·9 ±1·3	7·9 ±0·6
COCM	10	7·5 ±0·7	13·5 ±1·0	12·8 ±0·9	12·0 ±1·0	14·7 ±1·1	12·9 ±1·9	6·7 ±0·5
AS	10	13·7 ±1·0	15·9 ±1·1	16·3 ±0·8	16·8 ±1·0	16·8 ±1·3	16·7 ±1·0	8·7 ±1·5

* Abbreviations as in Table 1.

indicated that a statistically significant difference existed.

As a test for association between wall thickness and index scores in the left ventricle, mean values (averaged over sections) were computed for each heart. Spearman's correlation coefficient (R_S) was then used to measure association. In addition, for determining whether fibre disarray and fibrosis index scores varied with wall thickness within individual hearts, R_s was computed separately for each heart and then averaged over the 10 subjects in each diagnostic group. This provided the basis for a two-tailed t test for association.

In all cases, differences that were not significant at the $p = 0·05$ level have been termed "not statistically significant".

Results

For the purposes of comparing the severity and distribution of fibre disarray in hypertrophic and congestive cardiomyopathy and aortic stenosis with normal, indices were derived for each section location in each disease group. The most severe involvement with fibre disarray would have an index of 4·0, whereas if fibre disarray was absent, the index would be zero. Indices numerically less than unity occurred when fibre disarray was present in a section location in some hearts and absent in other hearts within the same group.

FIBRE DISARRAY

Normal (group 1)

Fibre disarray occurred in normal hearts, as previously reported,[18 19] in the right and left ventricles. The fibre disarray index varied from 0·5 in the anterior left ventricular wall to 0·9 in the posterior left ventricular wall (Table 3, Fig. 5).

Table 3 *Fibre disarray index for section locations 1 to 7 in four groups studied**

Group	*No. of hearts*	*Fibre disarray index for each section location (Fig. 1) (Mean and SE)*						
		Left ventricle						*Right ventricle*
		1	*2*	*3*	*4*	*6*	*7*	*5*
Normal	10	0·63 ±0·14	0·53 ±0·13	0·87 ±0·14	0·90 ±0·25	0·63 ±0·19	0·83 ±0·12	0·87 ±0·18
HOCM	10	1·93 ±0·13	1·50 ±0·22	1·43 ±0·13	1·10 ±0·14	1·53 ±0·20	1·30 ±0·20	0·97 ±0·15
COCM	10	0·80 ±0·21	0·77 ±0·21	0·77 ±0·17	0·77 ±0·16	0·67 ±0·17	1·20 ±0·19	0·97 ±0·24
AS	10	0·63 ±0·14	0·90 ±0·17	0·97 ±0·18	1·00 ±0·16	0·80 ±0·15	0·97 ±0·18	0·83 ±0·24

* Abbreviations as in Table 1.

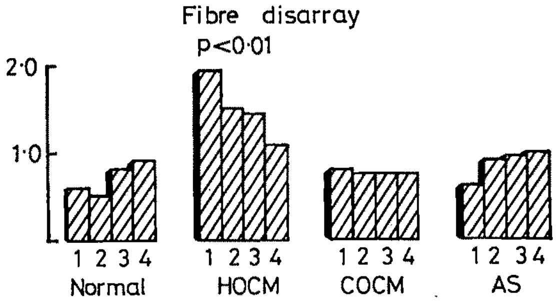

Fig. 5 *Mean of fibre disarray index for section locations 1 to 4 (Fig. 1) for normal hearts, hypertrophic cardiomyopathy (HOCM), congestive cardiomyopathy (COCM), and aortic stenosis (AS). Fibre disarray index was significantly increased in HOCM but was normal in COCM and AS.*

In the transverse axis of the left ventricle, the severity of the fibre disarray index was similar in section locations 1 to 4, and it did not differ significantly in the lower septum, lower lateral left ventricular wall, or right ventricular wall.

Hypertrophic cardiomyopathy (group 2)

In the hearts with hypertrophic cardiomyopathy, the fibre disarray index was significantly increased ($p < 0·001$). In the left ventricular transverse axis, it varied from 1·3 in the posterior wall to 2·0 in the upper septum (Table 3, Fig. 5). Though the fibre disarray index was consistently greater in the septum than in the free wall, the differences among sections were not statistically significant. The lack of a significant difference in fibre disarray index and, similarly, in the fibrosis index when section locations of the heart were compared does not mean that fibre disarray or fibrosis is homogeneous. It indicates that differences occurring within one heart were not consistently reproduced among other hearts and does not warrant the conclusion that no difference existed. A true difference could possibly exist and yet go undetected because of a relatively small sample size. In addition, the fibre disarray index was comparable in the lower and upper portions of the lateral wall and in the lower and upper parts of the septum; there was no change in severity from the apex to the base of the heart. The fibre disarray index in the right ventricle in hypertrophic cardiomyopathy was normal (Table 3).

Congestive cardiomyopathy (group 3)

The fibre disarray index in hearts with congestive cardiomyopathy varied from 0·7 in the lower lateral left ventricular wall to 1·2 in the lower septum and

1·0 in the right ventricle. There was no statistically significant variation in the severity of fibre disarray among the sections, and no statistically significant difference from the normal group was observed (Table 3, Fig. 5).

Aortic stenosis (group 4)

The fibre disarray index in the hearts with aortic stenosis varied from 0·6 in the upper septum to 1·0 in the posterior left ventricular wall and 0·8 in the right ventricle (Table 3, Fig. 5). These values were very similar to those in congestive cardiomyopathy and were not significantly different from normal in severity or distribution.

WALL THICKNESS

The fibre disarray index in the left ventricle varied independently of wall and septal thickness within the hearts with hypertrophic cardiomyopathy. In hearts with aortic stenosis, wall thickness was significantly increased ($p=0{\cdot}001$), similar to that in hypertrophic cardiomyopathy ($p<0{\cdot}001$) (Table 2); in the dilated hearts with congestive cardiomyopathy, in which wall thickness was normal, the fibre disarray index was the same as in aortic stenosis. Thus, these findings indicate that fibre disarray was unrelated to wall thickness, that is, to left ventricular hypertrophy.

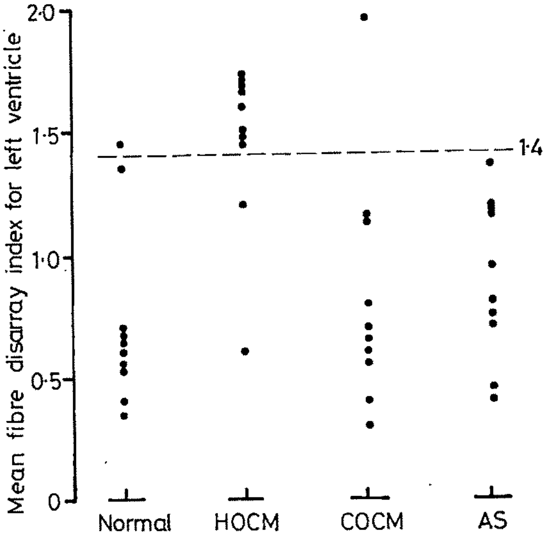

Fig. 6 *Mean fibre disarray index for entire left ventricle in each patient (computed for section locations 1 to 4 and 6 and 7, Fig. 1), in various groups, normals, HOCM, COCM, and AS (abbreviations as before). Reliability of fibre disarray index in separating hearts with HOCM from normals, COCM, and AS is indicated when an arbitrary value of 1·4 is used as a criterion. Two hearts with HOCM are missed and one normal and one COCM heart are incorrectly classified, but no heart with AS is misclassified.*

Table 4 *Microscopical scar index for section locations 1 to 7 in four groups studied**

Group	*No. of hearts*	*Microscopical scar index for each section location (Fig. 1) (Mean and SE)*						
		Left ventricle						*Right ventricle*
		1	*2*	*3*	*4*	*6*	*7*	*5*
Normal	10	0·20	0·07	0·00	0·03	0·00	0·00	0·00
		±0·16	±0·07	—	±0·03	—	—	—
HOCM	10	0·17	0·03	0·17	0·23	0·10	0·47	0·03
		±0·11	±0·03	±0·09	±0·14	±0·05	±0·21	±0·03
COCM	10	0·77	0·57	0·40	0·27	0·30	0·17	0·37
		±0·24	±0·18	±0·22	±0·17	±0·24	±0·10	±0·21
AS	10	0·10	0·40	0·23	0·33	0·17	0·63	0·17
		±0·10	±0·27	±0·17	±0·09	±0·13	±0·32	±0·11

* Abbreviations as in Table 1.

The reliability of the fibre disarray index in separating hearts with hypertrophic cardiomyopathy from normals, those with congestive cardiomyopathy, and those with aortic stenosis is indicated in Fig. 6. When 1·4 was used as an arbitrary criterion, two cases of hypertrophic cardiomyopathy were missed and one normal heart and one heart with congestive cardiomyopathy were incorrectly classified, but no case of aortic stenosis was misclassified.

MYOCARDIAL FIBROSIS

In a fashion exactly like that for the fibre disarray index, indices for each of the four types of fibrosis were derived so that hypertrophic and congestive cardiomyopathy and aortic stenosis could be compared with the normal and subsequently with one another.

MICROSCOPICAL SCARS

Microscopical scars were uncommon in normal hearts and were not significantly more common in hypertrophic or congestive cardiomyopathy or aortic stenosis in the right and left ventricles in each group (Table 4, Fig. 7).

INTERSTITIAL FIBROSIS

The interstitial fibrosis index in normal hearts varied little (0·4 to 0·9), and in hypertrophic cardiomyopathy (0·9 to 1·2) it did not differ significantly from normal in the right ventricle or the left ventricle. In congestive cardiomyopathy and aortic stenosis it was significantly ($p=0{\cdot}002$) increased, 1·3 to 2·0 and 1·4 to 1·8, respectively

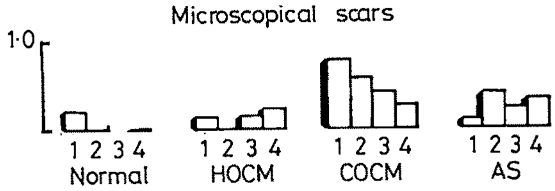

Fig. 7 *Mean of microscopical scar index in normals, HOCM, COCM, and AS (abbreviations as before), showing no significant increase from normal in HOCM, COCM, or AS.*

(Table 5, Fig. 8). Regardless of severity, the differences in interstitial fibrosis index among section locations within each group were not statistically significant.

PERIVASCULAR FIBROSIS

The perivascular fibrosis index in the normal heart was 0·6 to 1·0 in the left ventricle and 0·5 in the right ventricle; in hypertrophic cardiomyopathy it was 0·7 to 1·2 in the left ventricle and 0·6 in the right ventricle, and did not differ significantly from normal. In congestive cardiomyopathy and aortic stenosis, however, perivascular fibrosis indices in the left ventricle were significantly (p=0·001) increased, 1·5 to 1·8 and 1·3 to 1·7, respectively (Table 6, Fig. 9) but were not increased in the right ventricle (1·3 and 1·0). Within each group the differences in severity of perivascular fibrosis among section locations (that is, the distribution of perivascular fibrosis) throughout the left ventricle were not statistically significant.

PLEXIFORM FIBROSIS

Plexiform fibrosis occurred in the right ventricle and left ventricle of the hearts of all groups. The plexiform fibrosis index was 0·2 to 0·4 in normals, 0·2 to 0·6 in congestive cardiomyopathy, and 0·2 to 0·6 in aortic stenosis, and the distribution among section locations in the left and right ventricles in all three groups did not vary significantly (Table 7, Fig. 10). In hypertrophic cardiomyopathy, plexiform fibrosis was significantly increased, 0·5 to 1·1 (p=0·004), particularly in the septum, where its prevalence was closely associated with fibre disarray (Table 7, Fig. 10).

Table 5 *Interstitial fibrosis index for section locations 1 to 7 in four groups studied**

Group	*No. of hearts*	*Interstitial fibrosis index for each section location (Fig. 1) (Mean and SE)*						
		Left ventricle						*Right ventricle*
		1	*2*	*3*	*4*	*6*	*7*	*5*
Normal	10	0·90 ±0·23	0·47 ±0·15	0·80 ±0·23	0·93 ±0·22	0·43 ±0·14	0·73 ±0·25	0·80 ±0·23
HOCM	10	1·07 ±0·24	1·00 ±0·21	1·13 ±0·13	0·93 ±0·22	1·23 ±0·20	0·87 ±0·25	0·67 ±0·26
COCM	10	2·03 ±0·30	1·67 ±0·29	1·50 ±0·23	1·33 ±0·25	1·50 ±0·27	1·43 ±0·21	1·23 ±0·16
AS	10	1·57 ±0·28	1·47 ±0·29	1·67 ±0·31	1·80 ±0·27	1·37 ±0·35	1·83 ±0·30	1·20 ±0·22

* Abbreviations as in Table 1.

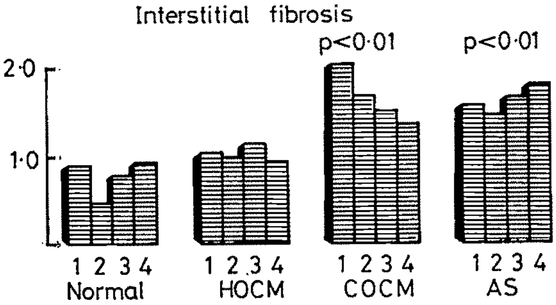

Fig. 8 *Mean of interstitial fibrosis index in normals, HOCM, COCM, and AS (abbreviations as before). Interstitial fibrosis index was normal in HOCM but was significantly increased in both COCM and AS.*

WALL THICKNESS

Wall thicknesses for each section location are shown in Table 2. The indices for all four types of fibrosis varied independently of wall thickness in the left ventricle, both among sections within individual hearts and among hearts within diagnostic groups.

Discussion

Most of the so-called diagnostic features of hypertrophic cardiomyopathy have subsequently been shown to occur also in unrelated anatomical and physiological circumstances; thus, no single clinical or histopathological feature of this disease is pathognomonic. A consistent observation in patients with this disease, however, is the wide spectrum of left ventricular function.[22–24] The purposes of our study were to determine the specificity of fibre disarray in hypertrophic cardiomyopathy, to quantify the severity and distribution of fibre disarray and myocardial fibrosis and their relation to left ventricular hypertrophy in the heart as a whole, and to establish whether an anatomico-pathological basis could be found to account for the variability in left ventricular function.

Myocardial fibre disarray, which had initially been believed by some investigators to be specific for hypertrophic cardiomyopathy,[1 13 14] has been shown in normal hearts,[18 19] and in a variety of congenital cardiac malformations,[18 20 29 30] in which there appears to be no common pathophysiological mechanism for this change. The non-specific nature of fibre disarray was confirmed in our study, in that it was present in varying degrees in normal hearts and in hearts with congestive cardiomyopathy and aortic stenosis and was similarly distributed among section locations throughout the long and short axes of the left ventricle. Furthermore, the fibre disarray index in the right ventricular wall did not vary significantly among the three disease groups (2 to 4).

In hypertrophic cardiomyopathy, the fibre disarray index was significantly increased in all section locations in the transverse axis of the left ventricle 1 cm below the mitral valve, in the lower lateral left ventricular wall, and in the lower septum. Though the fibre disarray index in hypertrophic cardiomyopathy was numerically slightly higher in the septum than in the free wall, this difference was not significant, in distinct contrast to all the previous qualitative studies.[13 14 30 31] In addition, the fibre disarray index varied independently of wall and septal thickness; this indicated that asymmetric septal hypertrophy is not a prerequisite for fibre disarray. The fibre disarray index in the right ventricle in hypertrophic cardiomyopathy was no different from that in the right ventricle of normal hearts.

Fibre disarray occurred most commonly in the middle third of the septum and free wall (Fig. 2), but this may be explained by the greater facility with which it can be recognised when sections of myocardium are cut parallel to, rather than at right angles to, the myocardial fibre axis. Though fibre disarray *per se* is non-specific, its value as a histological marker was greatly enhanced when both its severity and its distribution within the left ventricle were quantified. When an arbitrary value of 1·4 was selected, it allowed separation of hearts with hypertrophic cardiomyopathy from normal hearts and also from those with aortic stenosis and congestive cardiomyopathy (Fig. 6).

Table 6 *Perivascular fibrosis index for section locations 1 to 7 in four groups studied**

Group	No. of hearts	*Perivascular fibrosis index for each section location (Fig. 1) (Mean and SE)*						
		Left ventricle						*Right ventricle*
		1	*2*	*3*	*4*	*6*	*7*	*5*
Normal	10	1·00 ±0·17	0·87 ±0·11	0·93 ±0·13	0·90 ±0·12	0·63 ±0·20	0·80 ±0·11	0·53 ±0·21
HOCM	10	1·17 ±0·18	0·73 ±0·14	1·10 ±0·12	1·23 ±0·17	1·03 ±0·22	1·13 ±0·20	0·60 ±0·16
COCM	10	1·53 ±0·22	1·67 ±0·14	1·77 ±0·28	1·47 ±0·29	1·47 ±0·22	1·67 ±0·12	1·27 ±0·25
AS	10	1·67 ±0·19	1·43 ±0·22	1·63 ±0·22	1·47 ±0·13	1·30 ±0·25	1·57 ±0·19	1·00 ±0·26

* Abbreviations as in Table 1.

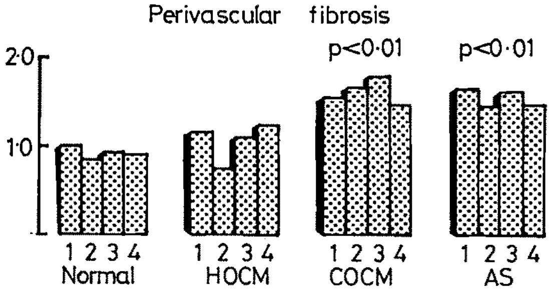

Fig. 9 *Mean of perivascular fibrosis in normals, HOCM, COCM, and AS (abbreviations as before). Perivascular fibrosis index was normal in HOCM but was significantly increased in COCM and AS.*

Of the four types of myocardial fibrosis that were independently assessed, none was specific for hypertrophic cardiomyopathy. In hearts with hypertrophic cardiomyopathy and aortic stenosis, obstruction to left ventricular outflow had resulted in a similar degree of left ventricular hypertrophy, as determined by heart weight and wall thickness. The fact that perivascular and interstitial fibrosis indices were normal in hypertrophic cardiomyopathy but were significantly increased in aortic stenosis suggested that though both groups had left ventricular outflow tract obstruction, different pathophysiological mechanisms were at work.

The perivascular and interstitial fibrosis indices in aortic stenosis and congestive cardiomyopathy were similarly and significantly increased, though wall thickness was normal in congestive cardiomyopathy and significantly increased in aortic stenosis; these findings suggest that these types of fibrosis vary independently of left ventricular hypertrophy. Within all three disease entities (groups 2 to 4), differences in severity of interstitial and perivascular fibrosis among section locations (that is, distribution of these variables) were not statistically significant in the left ventricle. Microscopical scars, which represent replacement of myocardial fibres after cell death, were present in all four groups and the scar index was normal. A further form of myocardial fibrosis, plexiform fibrosis, occurred in all hearts, and it had a similar magnitude and distribution in normal hearts, congestive cardiomyopathy, and aortic stenosis. It was significantly increased, however, in hypertrophic cardiomyopathy in which it was closely related to fibre disarray.

There is controversy about the cause of fibre disarray in hypertrophic cardiomyopathy. One suggestion has been that the aetiological mechanism is increased wall stress and prolonged isometric contraction,[13 20] for both occur in hypertrophic cardiomyopathy and semilunar valve atresia, in which fibre disarray of a similar severity has been reported.[18] Stress, however, can be mathematically defined as force per unit area, and in the intact heart it equals transmural pressure. Because normal pericardial pressure in man is low (0 to 5 mmHg),[32] peak transmural pressure (that is, peak wall stress) closely approximates peak left ventricular pressure. There are no data to support the suggestion[18] that there is a correlation between left ventricular pressure (wall stress) and fibre disarray in hypertrophic cardiomyopathy.

Although we had no haemodynamic data and therefore could not measure wall stress, we attempted to test indirectly the hypothesis that wall stress resulted in fibre disarray. We selected hearts with left ventricular outflow tract obstruction caused by aortic stenosis with a similar degree of left ventricular hypertrophy (wall thickness and heart weight) to the hearts with hypertrophic cardiomyopathy. The fibre disarray index in hearts with aortic stenosis was significantly less than that in hypertrophic cardiomyopathy, and this indicated that though increased wall stress (that is, increased left ventricular pressure) had "produced" a similar degree of left ventricular hypertrophy, it had not resulted in increased myocardial fibre disarray. Furthermore, in some patients with hypertrophic cardiomyopathy, left ventricular outflow tract gradients are absent at rest and remain small even on pharmacological provocation; consequently, left ventricular pressure and, therefore, wall stress must be close to normal. Fibre disarray has not been reported to be less of a histological marker in patients with small or absent left ventricular outflow pressure gradients than it is in those with large pressure gradients. There is thus little evidence to suggest a relation between fibre disarray and wall stress, and further support for this lack of relation is provided by the existence of fibre disarray in normal hearts and in those with congestive cardiomyopathy.

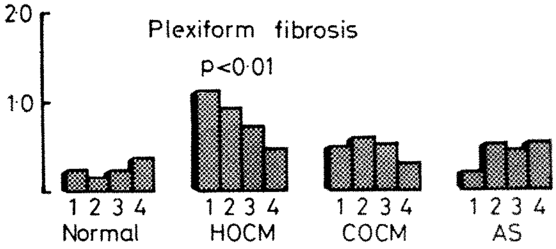

Fig. 10 *Mean of plexiform fibrosis index in normals, HOCM, COCM, and AS (abbreviations as before). Plexiform fibrosis index was significantly increased in HOCM but was normal in COCM and AS.*

Table 7 *Plexiform fibrosis index for section locations 1 to 7 in four groups studied**

Group	*No. of hearts*	*Plexiform fibrosis index for each section location (Fig. 1) (Mean and SE)*						
		Left ventricle						*Right ventricle*
		1	*2*	*3*	*4*	*6*	*7*	*5*
Normal	10	0·23 ±0·11	0·23 ±0·11	0·13 ±0·07	0·37 ±0·18	0·17 ±0·13	0·17 ±0·09	0·13 ±0·13
HOCM	10	1·13 ±0·16	0·93 ±0·28	0·70 ±0·10	0·47 ±0·19	0·63 ±0·14	0·53 ±0·15	0·33 ±0·14
COCM	10	0·50 ±0·14	0·60 ±0·27	0·53 ±0·17	0·23 ±0·11	0·27 ±0·14	0·37 ±0·14	0·23 ±0·13
AS	10	0·20 ±0·09	0·53 ±0·17	0·47 ±0·23	0·57 ±0·16	0·43 ±0·19	0·43 ±0·21	0·20 ±0·20

* Abbreviations as in Table 1.

An alternative hypothesis has been that contraction-induced linear forces may be important during cardiogenesis in producing normal myocardial fibre architecture and fibre alignment,[33] as they appear to be in the development of other biological tissue such as bone, and that in hypertrophic cardiomyopathy alteration in these directional forces interferes with the parallel alignment of myocardial fibres and results in fibre disarray.[20] This hypothesis, however, does not explain the presence of fibre disarray in normal hearts, nor how it can be induced secondarily in normal animals long after cardiogenesis by the administration of nerve growth factor[34] or by chronic endocardial pacing.[21] For the present, the implication that the fibre disarray in patients with hypertrophic cardiomyopathy who first have cardiovascular symptoms in their sixth or seventh decade has been present since before birth remains conjectural.

A further hypothesis as to the cause of fibre disarray in hypertrophic cardiomyopathy is that it develops because of a primary genetic predisposition,[35] which could explain its presence in a small number of reported cases of this disease at or soon after birth[36] and also its absence in nonfamilial asymmetric septal hypertrophy.[31 37] This hypothesis, however, does not account for the presence of fibre disarray in semilunar valve atresia[18] and in the conus muscularis of patients with tetralogy of Fallot,[18 30] conditions that are not genetically determined.

We were also unable to explain the presence of fibre disarray in congestive cardiomyopathy but noted that it was significantly more common than in normal hearts throughout the left ventricle, was not significantly more severe in the septum than in the free wall, varied independently of left ventricular hypertrophy, and appeared unrelated to left ventricular wall stress. The fibre disarray index was useful in distinguishing hypertrophic from congestive cardiomyopathy and aortic stenosis when an arbitrary value of $\geqslant 1{\cdot}4$ was chosen (Fig. 6). Interstitial and perivascular forms of fibrosis were normal in hypertrophic cardiomyopathy, but plexiform fibrosis, which was closely associated with myocardial fibre disarray, occurred significantly more often in hearts with hypertrophic cardiomyopathy than in hearts with congestive cardiomyopathy or aortic stenosis. We could not demonstrate a pathological basis in terms of either fibre disarray or fibrosis on which to explain the variability of left ventricular function as shown echocardiographically and angiocardiographically, but this may have been because of the fact that the death of the patients with hypertrophic cardiomyopathy was directly related to left ventricular disease and that the left ventricular free wall and septal myocardium may have reached a similar degree of end-stage cardiomyopathy.

Fibre disarray is thus a non-specific histological feature, as indicated by its presence in normal hearts, aortic stenosis, congestive cardiomyopathy, and a heterogeneous group of congenital cardiac malformations with no common aetiological mechanism. Confusion may have arisen because a solitary causal mechanism has been sought; it probably represents a pathway for diverse pathophysiological processes.

References

1 Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J* 1958; **20:** 1–8.

2 Brock R. Functional obstruction of the left ventricle (acquired aortic subvalvar stenosis). *Guy Hosp Rep* 1957; **106:** 221–38.

3 Goodwin JF, Hollman A, Cleland WP, Teare D. Obstructive cardiomyopathy simulating aortic stenosis. *Br Heart J* 1960; **22:** 403–14.

4 Braunwald E, Lambrew CT, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic hypertrophic subaortic stenosis. I. A description of the disease based upon an analysis of 64 patients. *Circulation* 1964; **29,** suppl 4: 3–119.

5 Cohen J, Effat H, Goodwin JF, Oakley CM, Steiner RE. Hypertrophic obstructive cardiomyopathy. *Br Heart J* 1964; **26:** 16–32.

6 Soulie P, Joly F, Carlotti J. Les sténoses idiopathiques de la chambre de chasse du ventricle gauche (à propos de 10 observations). *Acta Cardiol (Brux)* 1962: **17:** 335–78.

7 Shabetai R, McGuire J. Idiopathic cardiac hypertrophy simulating valvular heart disease. *Am Heart J* 1963; **65:** 124–30.

8 Henry WL, Clark CE, Epstein SE. Asymmetric septal hypertrophy: echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation* 1973; **47:** 225–33.

9 Henry WL, Clark CE, Epstein SE. Asymmetric septal hypertrophy (ASH): the unifying link in the IHSS disease spectrum; observations regarding its pathogenesis, pathophysiology, and course. *Circulation* 1973; **47:** 827–32.

10 Epstein SE, Henry WL, Clark CE, *et al.* Asymmetric septal hypertrophy. *Ann Intern Med* 1974; **81:** 650–80.

11 Shah PM, Gramiak R, Adelman AG, Wigle ED. Role of echocardiography in diagnostic and hemodynamic assessment of hypertrophic subaortic stenosis. *Circulation* 1971; **44:** 891–8.

12 Van Noorden S, Olsen EGJ, Pearse AGE. Hypertrophic obstructive cardiomyopathy, a histological, histochemical, and ultrastructural study of biopsy material. *Cardiovasc Res* 1971; **5:** 118–31.

13 Ferrans VJ, Morrow AG, Roberts WC. Myocardial ultrastructure in idiopathic hypertrophic subaortic stenosis: a study of operatively excised left ventricular outflow tract muscle in 14 patients. *Circulation* 1972; **45:** 769–92.

14 Maron BJ, Ferrans VJ, Henry WL, *et al.* Differences in distribution of myocardial abnormalities in patients with obstructive and nonobstructive asymmetric septal hypertrophy (ASH): light and electron microscopic findings. *Circulation* 1974; **50:** 436–46.

15 James TN, Marshall TK. De subitaneis mortibus. XII. Asymmetrical hypertrophy of the heart. *Circulation* 1975; **51:** 1149–66.

16 Bulkley BH, Fortuin NJ. Systolic anterior motion of the mitral valve without asymmetric septal hypertrophy. *Chest* 1976; **69:** 694–6.

17 Larter WE, Allen HD, Sahn DJ, Goldberg SJ. The asymmetrically hypertrophied septum: further differentation of its causes. *Circulation* 1976; **53:** 19–27.

18 Bulkley BH, Weisfeldt ML, Hutchins GM. Asymmetric septal hypertrophy and myocardial fiber disarray: features of normal, developing, and malformed hearts. *Circulation* 1977; **56:** 292–8.

19 Van der Bel-Kahn J. Muscle fibre disarray in common heart diseases. *Am J Cardiol* 1977; **40:** 355–64.

20 Bulkley BH, Weisfeldt ML, Hutchins GM. Isometric cardiac contraction: a possible cause of the disorganized myocardial pattern of idiopathic hypertrophic subaortic stenosis. *N Engl J Med* 1977; **296:** 135–9.

21 Adomian GE, Beazell JW, Furmanski M, Tan KS,

Laks MM. The production of myofibrillar disarray in hearts of normal dogs produced by chronic electronic pacing (abstract). *Circulation* 1977; **56,** suppl 3: 205.

22 St John Sutton MG, Tajik AJ, Gibson DG, Brown DJ, Seward JB, Giuliani ER. Echocardiographic assessment of left ventricular filling and septal and posterior wall dynamics in idiopathic hypertrophic subaortic stenosis. *Circulation* 1978; **57:** 512–20.

23 Sanderson JE, Traill TA, St John Sutton MG, Brown DJ, Gibson DG, Goodwin JF. Left ventricular relaxation and filling in hypertrophic cardiomyopathy. An echocardiographic study. *Br Heart J* 1978; **40:** 596-601.

24 Sanderson JE, Gibson DG, Brown DJ, Goodwin JF. Left ventricular filling in hypertrophic cardiomyopathy: an angiographic study. *Br Heart J* 1977; **39:** 661–70.

25 Davies MJ, Pomerance A, Teare RD. Pathological features of hypertrophic obstructive cardiomyopathy. *J Clin Pathol* 1974; **27:** 529–35.

26 Roberts WC, Ferrans VJ. Pathologic anatomy of the cardiomyopathies: idiopathic dilated and hypertrophic types, infiltrative types, and endomyocardial disease with and without eosinophilia. *Hum Pathol* 1975; **6:** 287–342.

27 Anderson KR, St John Sutton MG, Lie JT. Histopathological types of cardiac fibrosis in myocardial disease. *J Pathol* 1979; **128:** 78–85.

28 Anderson TW. *Introduction to multivariate statistical analysis.* New York: John Wiley & Sons, 1958.

29 Maron BJ, Ferrans VJ, White RI Jr, Unusual evolution of acquired infundibular stenosis in patients with ventricular septal defect: clinical and morphologic observations. *Circulation* 1973; **48:** 1092–103.

30 Jones M, Ferrans VJ, Morrow AG, Roberts WC. Ultrastructure of crista supraventricularis muscle in patients with congenital heart diseases associated with right ventricular outflow tract obstruction. *Circulation* 1975; **51:** 39–67.

31 Maron BJ, Edwards JE, Ferrans VJ, *et al.* Congenital heart malformations associated with disproportionate ventricular septal thickening. *Circulation* 1975; **52:** 926–32.

32 St John Sutton MG, Gibson DG. Measurement of postoperative pericardial pressure in man. *Br Heart J* 1977; **39:** 1–6.

33 Manasek FJ. Histogenesis of the embryonic myocardium. *Am J Cardiol* 1970; **25:** 149–68.

34 Witzke DJ, Kaye MP. Hypertrophic cardiomyopathy induced by administration of nerve growth factor (abstract). *Circulation* 1976; **54,** suppl 2: 88.

35 Clark CE, Henry WL, Epstein SE. Familial prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis. *N Engl J Med* 1973; **289:** 709–14.

36 Maron BJ, Edwards JE, Henry WL, Clark CE, Bingle GJ, Epstein SE. Asymmetric septal hypertrophy (ASH) in infancy. *Circulation* 1974; **50:** 809–20.

37 Maron BJ, Clark CE, Henry WL, *et al.* Prevalance and characteristics of disproportionate ventricular septal thickening in patients with acquired or congenital heart diseases: echocardiographic and morphologic findings. *Circulation* 1977; **55:** 489–96.

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Echocardiographic and anatomical correlates in the fetus*

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SUMMARY Fetal cardiac anatomy was studied in 200 pregnancies between 14 weeks' gestation and term using real time two-dimensional echocardiography. Eight scan planes were chosen as contributing valuable and distinct information on the establishment of cardiac normality. To confirm the echocardiographic interpretation, 25 fetal specimens between 12 and 28 weeks' gestational age were sectioned to imitate echocardiographic scan planes and the echocardiographic and anatomical pictures obtained were correlated with each other. The number of patients in whom each plane was recognised was tabulated in the first and second hundred, the second hundred having been studied after the anatomical studies were made. One longitudinal and one transverse plane could be seen in nearly all patients and considerable improvement in the frequency of recognition of other planes was made in the second hundred patients with increasing experience and anatomical understanding. The tricuspid-pulmonary and four-chamber planes alone, however, showed four cardiac chambers, two atrioventricular valves, and two arterial valves within their respective outflow tracts.

Because of the improved resolution and penetration of modern real time cross-sectional ultrasound scanners it has become possible to study cardiac anatomy during intrauterine life. This has important diagnostic and therapeutic implications for the future prenatal detection of congenital cardiac malformations. Because the fetal heart is surrounded by fluid-filled and airless lungs, which do not obstruct ultrasound, the heart is visualised in planes unobtainable in the neonate. The anatomy thus displayed is therefore different from that obtained with standard neonatal echocardiographic views, and that difference could allow misinterpretation of normal findings. In this study we have correlated anatomical and echocardiographic sections to confirm the echocardiographic interpretation and provide the basis for the detection of cardiac abnormalities.

Patients and methods

Two hundred pregnancies were scanned using a Kretz Combison 100 sector scanner or an ATL mark 3 sector scanner. The pictures were recorded on a Sanyo VTC 7100 videocassette recorder and subsequently analysed. The fetal position was established initially by visualising the spine longitudinally from the head to the sacrum (a sagittal section). Having established the fetal spine as the reference point, it was found that each of four planes in the longitudinal axis of the fetus provided slightly different information about the cardiac structures to be identified (Fig. 1). By turning the transducer through 90° from the longitudinal plane the fetus was then examined in the transverse axis (Fig. 2). Scanning in four transverse planes again augmented information about cardiac anatomy.

ANATOMICAL STUDIES

Twenty-five abortuses between 12 and 28 weeks' gestation were sectioned to imitate the postulated echocardiographic planes. The specimens were taken from a museum collection of spontaneous abortions which had been fixed in formalin. In several instances more than one section was required before the correct orientation was discovered.

Results

The first observation was that the fetal heart lies

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in a more horizontal plane than the neonatal heart (Fig. 3). This is because of the size of the liver, which in the fetus extends to the left side of the abdominal wall. Thus, the apex of the heart is displaced cranially and the long axis of the left ventricle is more horizontal than in the adult.

LONGITUDINAL PLANES

The most consistently obtained plane echocardiographically in the longitudinal axis (Fig. 4) shows that the pulmonary valve is anterior and cranial to the aortic root. The aortic valve is easily visualised cranial to the tricuspid valve as the latter enters the right ventricle from the right atrium. The right atrium is recognised by identifying its connection to the superior and inferior vena cavae. It was found that this plane of anatomy, termed the tricuspid-pulmonary plane, was produced by cutting the abortus parallel to the spinal cord with about 20° obliquity to the coronal plane, the plane being well anterior relative to the thoracic cavity (Fig. 1). The tricuspid-pulmonary plane was identified in 90 per cent of the first and 96 per cent of the second hundred patients studied. Having obtained this standard view, the angle of the transducer was then altered to obtain further longitudinal planes. By increasing the obliquity from the sagittal plane the pulmonary trunk can be shown sweeping posteriorly and connecting via the ductus arteriosus with the descending aorta (Fig. 5).

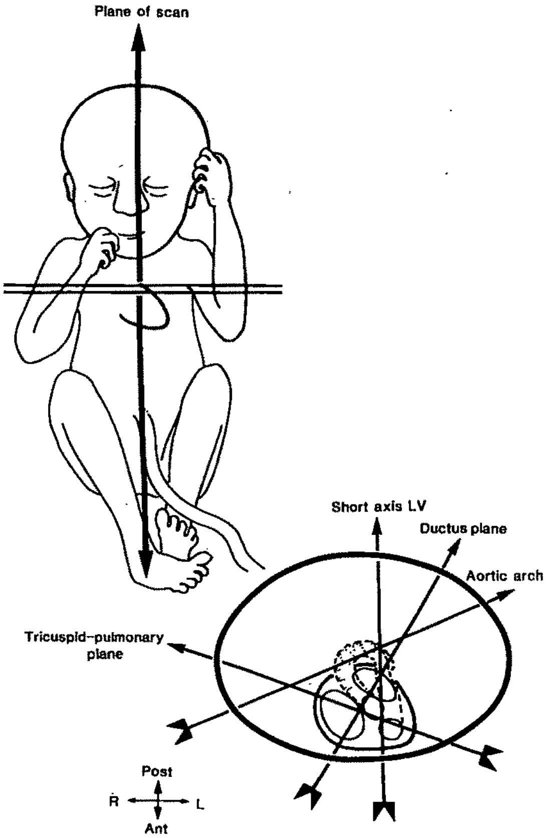


Fig. 1 *Diagram showing the four different planes all taken in the longitudinal axis of the fetus. The inset is a transverse section of the thorax showing the approximate orientation needed to produce the four different planes.*

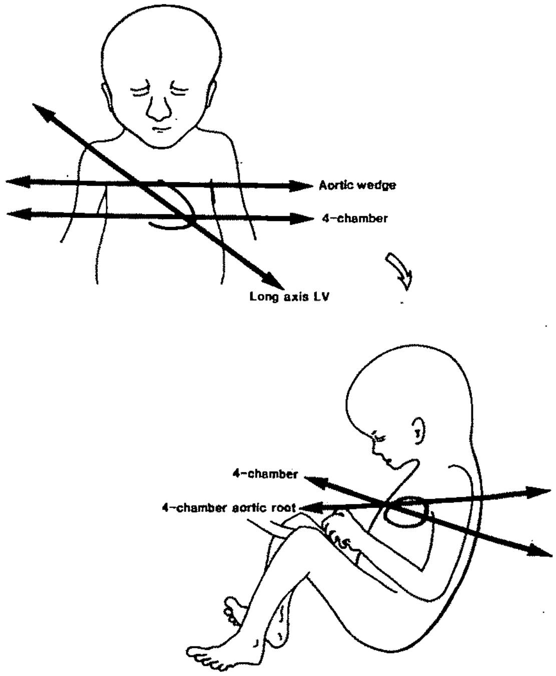


Fig. 2 *Diagram showing the four different planes in the transverse plane of the fetus. The aortic wedge and the four-chamber planes are direct transverse cuts. The four-chamber aortic root plane is obtained in the same transverse plane as the four-chamber but with cephalic angulation of the beam as shown in the lower right-hand diagram. The long axis of the left ventricle is obtained as an oblique plane as shown in the upper left-hand diagram.*

The aortic root is seen as a circle with the aortic valve closing at its centre and the right atrioventricular junction is well visualised. This plane is called the ductus plane. If instead of following the pulmonary trunk back to the ductus the angulation of the transducer to the sagittal plane is increased, the aortic arch can be traced

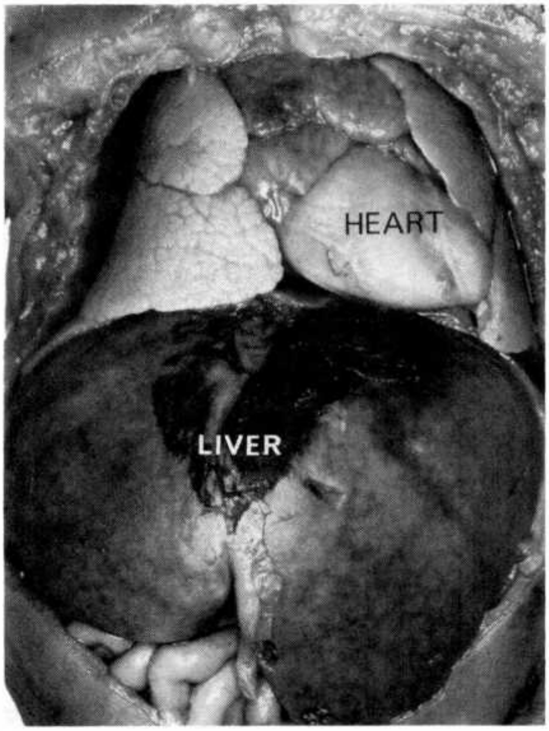


Fig. 3 *The thorax and abdomen of an 18-week human abortus dissected to show the orientation of the heart in relation to the remaining organs.*

into the descending aorta. The head and neck arteries are seen ascending from the arch and the relation to the oesophagus is seen (Fig. 6). This is the aortic arch plane. By then cutting the thorax in a sagittal plane taken to the left of the sternum with a slight degree of obliquity towards the left shoulder, the left ventricle is seen in its short axis with the right ventricular infundibulum ascending anterosuperiorly. The pulmonary valve is visualised in this plane (Fig. 7). We have called this the left ventricular short axis plane. The degree of success in obtaining these three additional longitudinal planes in the first and second hundred patients studied is shown in Tables 1 and 2.

TRANSVERSE PLANES

When the fetus is scanned in its transverse axis (Fig. 2) the view most consistently obtained shows the four-chamber view of the heart (Fig. 8). The right ventricle is seen anterior to the left ventricle, and its thinner wall and coarser trabecular pattern are often distinguishable. The anatomical cut to produce this plane was found to be completely transverse at the level of the junction of the sternum and the fifth costal cartilage. A similar transverse cut at the level of the manubrio-sternal junction (Fig. 2) shows the aorta wedged between the right and left atria and hence is termed the aortic wedge plane. The right and left ventricle are seen considerably foreshortened anterior to the aorta

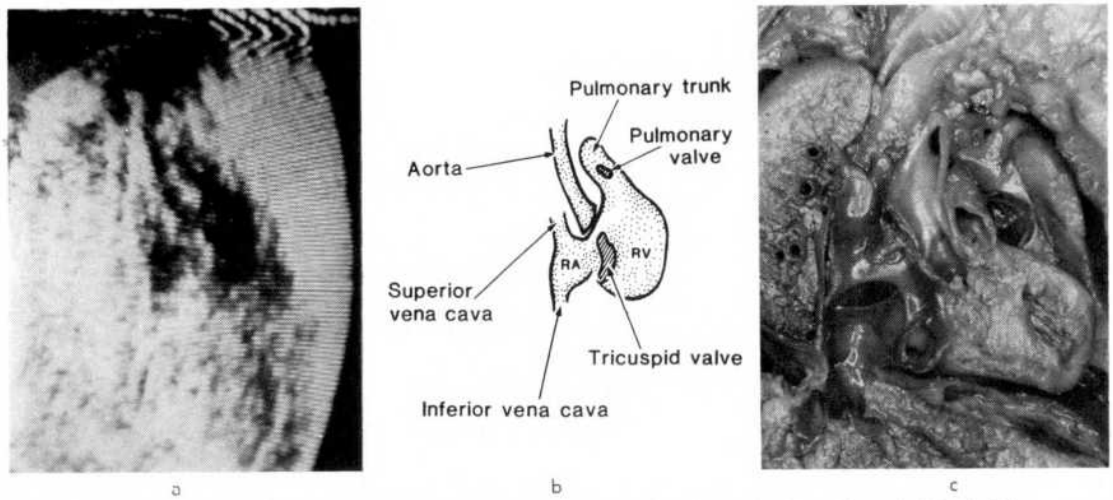


Fig. 4 *The longitudinal echocardiographic findings* (a) *in the tricuspid-pulmonary plane shown in Fig. 1. The drawing* (b) *shows the structures visualised, and* 4c *shows the simulated plane in a dissected human abortus.*

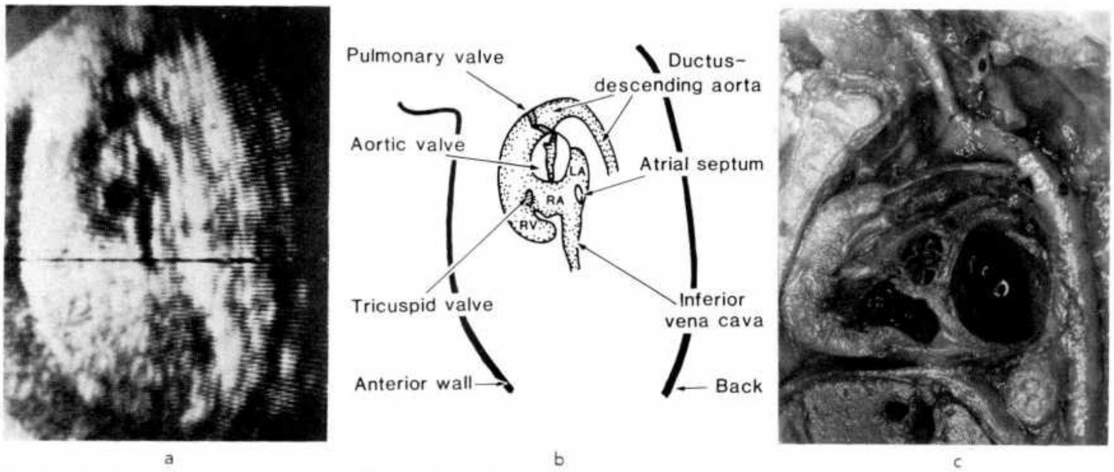


Fig. 5 *A similar composite of echocardiographic findings* (a), *drawing* (b), *and anatomical dissection* (c) *illustrating the ductus longitudinal plane as shown in Fig. 1.*

(Fig. 9). By adding cranial obliquity to the transverse plane at the level of the fifth costal cartilage the aortic root is seen in four chamber projection originating from the left ventricle, giving the four-chamber aortic root plane (Fig. 10). Finally, by taking a transverse plane with some obliquity away from the horizontal (Fig. 2) towards the right shoulder it is possible to cut the left ventricle in its long axis, giving the left ventricular long axis plane. The infundibulum of the right ventricle is then seen anteriorly, and the origin of the aortic root from the left ventricle, with aortic-mitral continuity, is visualised (Fig. 11). The success rate of obtaining these transverse planes is shown in Tables 1 and 2. The four-chamber plane was obtained in all of the first 100 patients studied and all of the subsequent patients. The left ventricular long axis plane showing its outflow tract was found only five times in the first 100 but in 41 per cent of the second 100 patients examined.

It may be seen from the Tables that some scan planes were easier to obtain at different gestational

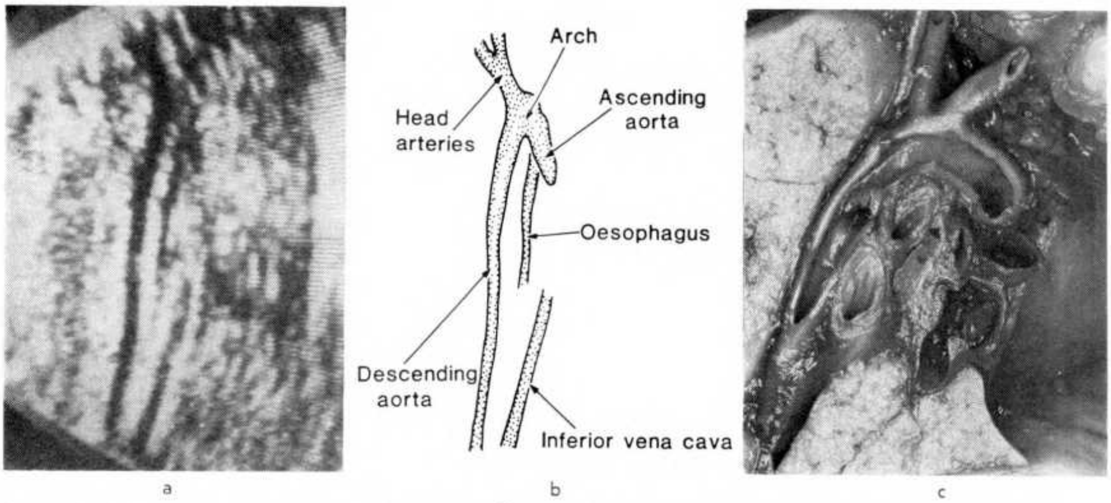


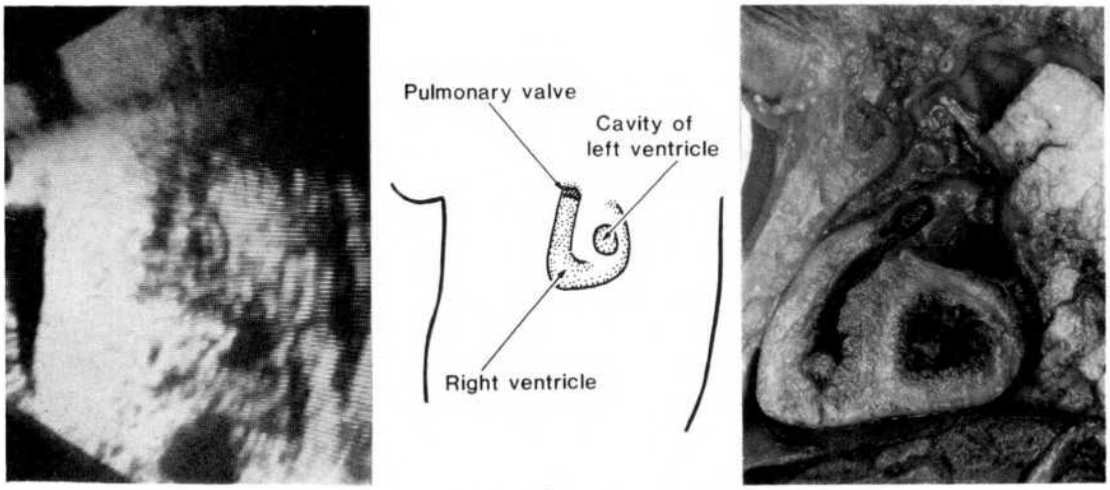
Fig. 6 *A similar composite as shown in Fig. 4 and 5, this time illustrating the aortic arch plane shown in Fig. 1.*

Table 1 *Plane recognition throughout pregnancy in first 100 patients*

Gestational age (wk)		14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Number of patients		2	2	11	3	11	4	10	5	5	3	6	2	1	1	3
	(%)	100	100	82	100	91	100	80	100	100	100	83	100	100	100	100
Tricuspid-pulmonary plane		2	2	9	3	10	4	8	5	5	3	5	2	1	1	3
	(%)	—	—	27	33	36	25	50	80	40	66	83	50	—	100	100
Ductus plane		—	—	3	1	4	1	5	4	2	2	5	1	—	1	3
	(%)	—	—	—	—	9	—	30	—	—	—	17	—	100	—	—
Aortic arch plane		—	—	—	—	1	—	3	—	—	—	1	—	1	—	—
	(%)	—	—	—	—	—	25	10	20	20	33	17	50	—	—	—
Short axis left ventricle		—	—	—	—	—	1	1	1	1	1	1	1	—	—	—
	(%)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Four-chamber plane		2	2	11	3	11	4	10	5	5	3	6	2	1	1	3
	(%)	—	—	27	66	91	25	60	80	40	100	50	—	100	100	66
Aortic wedge plane		—	—	3	2	10	1	6	4	2	3	3	—	1	1	2
	(%)	—	—	9	—	18	50	30	40	20	33	50	50	100	100	30
Four-chamber aortic root plane		—	—	1	—	2	2	3	2	1	1	3	1	1	1	1
	(%)	—	—	—	—	—	—	—	—	—	—	17	—	—	—	—
Long axis of left ventricle		—	—	—	—	—	—	—	—	—	—	1	—	—	—	—

Table 2 *Plane recognition throughout pregnancy in second 100 patients*

Gestational age (wk)		14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Number of patients		3	1	5	11	11	4	6	4	4	6	4	2	2	—	4
	(%)	100	100	100	100	100	100	100	100	100	100	100	50	100	—	100
Tricuspid-pulmonary plane		3	1	5	11	11	4	6	4	4	6	4	1	2	—	4
	(%)	33	100	80	82	91	100	66	75	100	83	100	50	100	—	100
Ductus plane		1	1	4	9	10	4	4	3	4	5	4	1	2	—	4
	(%)	33	—	20	55	73	50	50	50	100	33	75	0	0	—	100
Aortic arch plane		1	—	1	6	8	2	3	2	4	2	3	—	—	—	4
	(%)	33	—	40	36	45	50	33	100	75	66	50	100	50	—	75
Short axis left ventricle		1	—	2	4	5	2	2	4	3	4	2	2	1	—	3
	(%)	100	100	100	100	100	100	100	100	100	100	100	100	100	—	100
Four-chamber plane		3	1	5	11	11	4	6	4	4	6	4	2	2	—	4
	(%)	100	100	40	82	82	75	83	75	50	83	75	—	100	—	50
Aortic wedge plane		3	1	2	9	9	3	5	3	2	5	3	—	2	—	2
	(%)	66	100	60	82	91	100	100	100	100	100	100	100	100	—	100
Four-chamber aortic root plane		2	1	3	9	10	4	6	4	4	6	4	2	2	—	4
	(%)	0	0	20	27	18	25	66	25	50	83	50	0	0	—	50
Long axis of left ventricle		—	—	1	3	2	1	4	1	2	5	2	—	—	—	2



a b c

Fig. 7 *A composite showing the left ventricular short axis plane. See Fig. 1 for orientation.*

29	30	31	32	33	34	35	36	37	38	39	40	
5	2	2	3	—	8	5	2	1	2	1	—	100
100	100	100	66	—	75	100	100	100	50	100		
5	2	2	2	—	6	5	2	1	1	1	—	90
60	100	100	66	—	38	80	—	100	—	100	—	
3	2	2	2	—	3	4	—	1	—	1	—	50
40	50	50	66	—	25	40	50	—	—	100	—	
2	1	1	2	—	2	2	1	—	—	1	—	18
—	—	—	—	—	—	40	—	—	—	—	—	
—	—	—	—	—	—	2	—	—	—	—	—	92
100	100	100	100	—	100	100	100	100	100	100	—	
5	2	2	3	—	8	5	2	1	2	1	—	100
60	50	100	33	—	75	40	—	—	50	100		
3	1	2	1	—	6	2	—	—	1	1	—	55
100	100	100	100	—	63	80	100	100	50	100	—	
5	2	2	3	—	5	4	2	1	1	1		45
20	—	—	—	—	12·5	20	—	100	—	—	—	
1	—	—	—	—	1	1	—	1	—	—	—	5

29	30	31	32	33	34	35	36	37	38	39	40	
4	2	3	4	2	10	2	2	3	1	—	—	100
100	100	100	100	100	80	50	100	100	100	—	—	
4	2	3	4	2	8	1	2	3	1	—	—	96
75	100	33	50	100	70	50	100	66	100			
3	2	1	2	2	7	1	2	2	1	—	—	79
50	50	33	75	100	50	50	50	33	—	—	—	
2	1	1	3	2	5	1	1	1	—	—	—	53
75	100	66	75		40	100	50	66				
3	2	2	3	—	4	2	1	2	—	—	—	54
100	100	100	100	100	100	100	100	100	100	—	—	
4	2	3	4	2	10	2	2	3	1	—	—	100
75	50	100	75	100	60	50	100	33	100	—	—	
3	1	3	3	2	6	1	2	1	1	—	—	72
100	100	33	100	100	90	100	100	100	100			
4	2	1	4	2	9	2	2	3	1	—	—	91
50	50	33	50	100	70	100	0	33	0	—	—	
2	1	1	2	2	7	2	—	1	—	—	—	41

ages—for example, the short axis left ventricular plane after 20 weeks' gestation. It should be pointed out that the frequency of plane recognition reflects the speed and ease of their identification, and a higher detection rate could have been achieved if unlimited time had been available or if a repeat study had been performed in individuals. This is because fetal position or fetal movement may limit the number of planes identified at one particular time. In addition, scan plane identification is really an artificial way of dividing up what is a continuous scan sweep, which, with experience, allows each view to follow on from one another.

Discussion

The ability to recognise with accuracy normal cardiac anatomy by fetal echocardiography is a prerequisite for the successful antenatal diagnosis of congenital cardiac malformations. We have shown that this anatomy is displayed in a significantly different fashion in the fetus as compared with standard paediatric and adult echocardiographic sections. The reasons for this are twofold. First the heart is surrounded by fluid-filled lungs which, unlike the situation in extrauterine life, do not obstruct ultrasound. Second, the orientation of the heart is different, particularly in the middle trimester, because of the relatively large size of the liver, the major haemopoietic organ of the fetus. This tilts the apex of the heart cephalad and produces a more horizontal long axis of the left ventricle than is usually seen in the neonate.

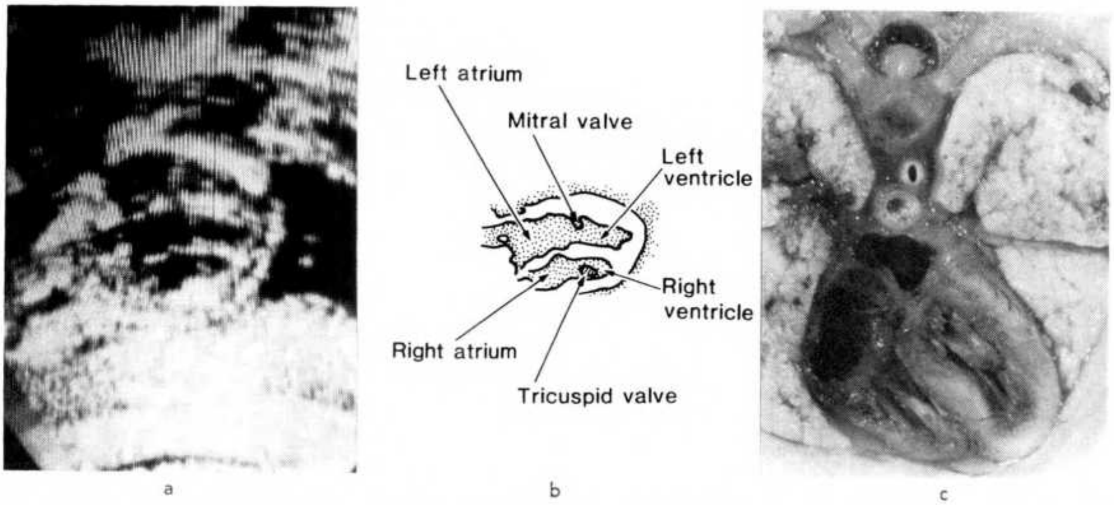


Fig. 8 *A composite of echocardiogram* (a), *drawing* (b), *and dissection* (c) *illustrating the findings in the four-chamber transverse plane (see Fig. 2). The left ventricle is dissected anterior to the annulus of the mitral valve.*

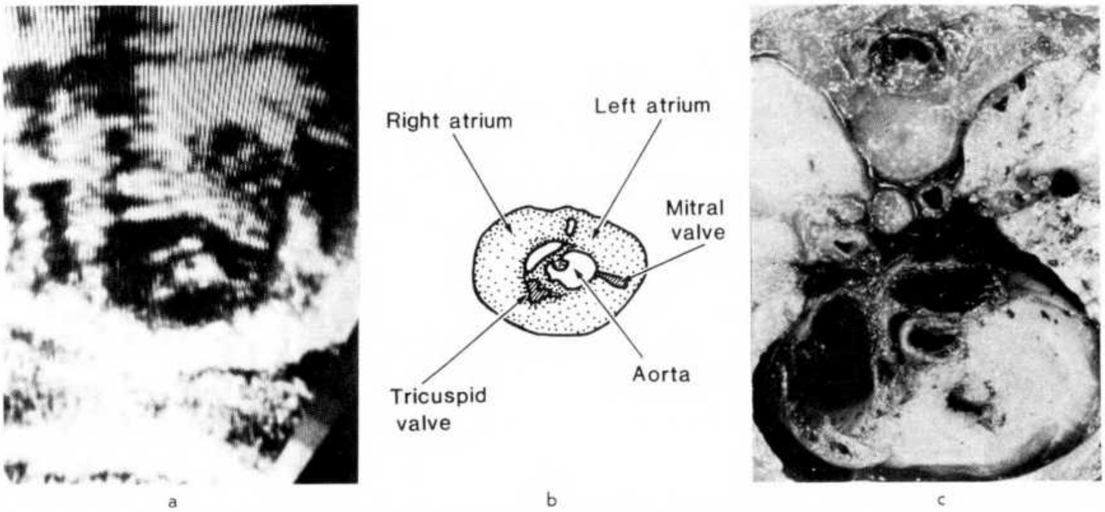


Fig. 9 *A composite showing the findings in the transverse plane which gives the aortic wedge echocardiographic cut (see Fig. 2).*

Perhaps because of this, the most easily obtained view in extrauterine life, namely the long axis section of the left ventricle, was the view most difficult to obtain during fetal life. The most consistently obtained longitudinal view showed the relation of tricuspid and pulmonary valves relative to the aortic valve while the most easily obtained transverse section disclosed the four-chamber arrangement of the right and left sides of the heart. By angulation of the ultrasound beam from these readily obtained scan planes, it was then possible to show with a high degree of accuracy the connection of the aorta to the left ventricle and the pulmonary trunk to the right ventricle. Thus, in all the patients studied, by using combinations of our described scan planes, it was possible to determine unequivocally the normality of the cardiac connections. Cardiac morphology can, we believe, be assessed with a high degree of accuracy though minor degrees of stenosis or obstruction

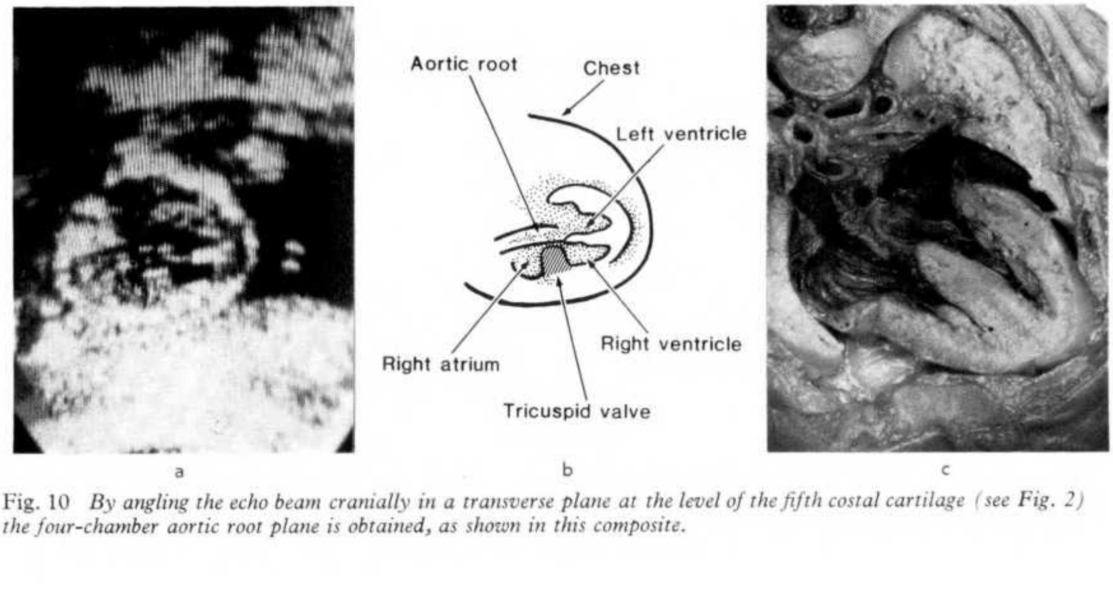


Fig. 10 *By angling the echo beam cranially in a transverse plane at the level of the fifth costal cartilage (see Fig. 2) the four-chamber aortic root plane is obtained, as shown in this composite.*

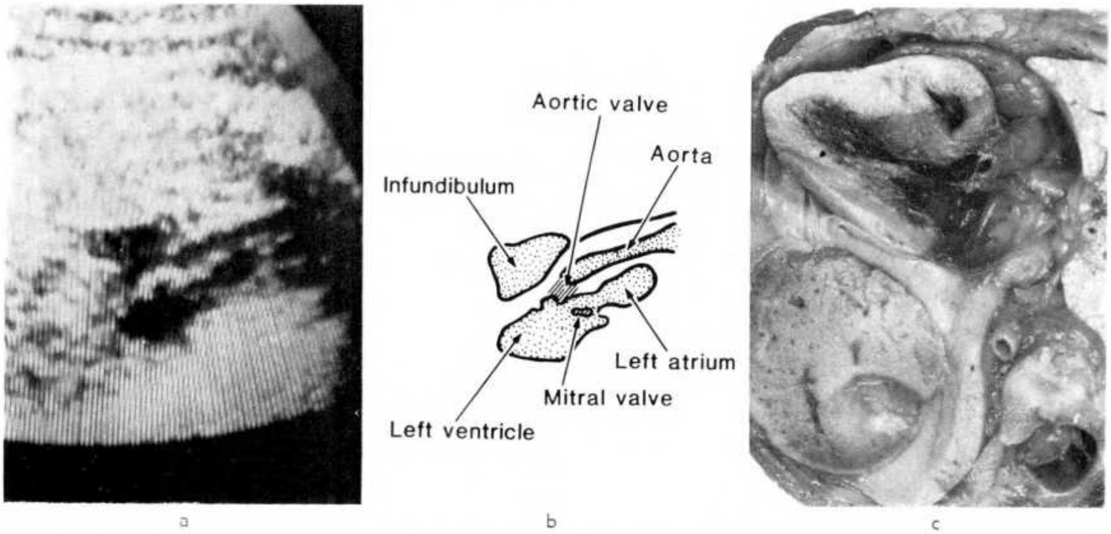


Fig. 11 *An oblique cut in the transverse plane as illustrated in Fig. 2 gives the long axis plane of the left ventricle, as shown in this composite.*

to ventricular outflow tracts may not be detected.

Despite these minor limitations concerning precise morphology, our findings show that many congenital lesions should be detectable between 20 and 30 weeks' gestation. A four-chamber scan alone should exclude hypoplasia of the right or left ventricles, univentricular heart with double inlet or absent connection, and the various forms of atrioventricular defects.

Normal scan planes showing the aortic root and pulmonary trunk ductus axis should exclude aortic and pulmonary atresia and truncus arteriosus. The four-chamber plane with the aortic root and the long axis plane of the left ventricle showed aortic-mitral and aortic-septal continuity with the attendant implications of these positive findings. Combinations of all the planes should allow the demonstration of normal intracardiac anatomy while the views obtained of the aortic and pulmonary artery may exclude anomalies of these vessels such as hypoplasia of the aortic isthmus.

Tables 1 and 2 show clearly the progress obtained with practice. In part the greater success obtained in the study of the second 100 patients was related to increased scanning experience, but also to the increased knowledge of fetal cardiac anatomy. These findings show that it is possible to establish cardiac normality in the fetus and should make it possible to diagnose major congenital cardiac malformations.

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Cardiovascular malformations in DiGeorge syndrome (congenital absence or hypoplasia of the thymus)

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SUMMARY Partial or complete absence of the thymus (DiGeorge syndrome, III-IV pharyngeal pouch syndrome) is often associated with agenesis or hypoplasia of the parathyroid glands and, almost invariably, with cardiovascular malformations. The clinical and pathological findings in 10 cases proven at necropsy are presented. All patients presented with cardiac symptoms and signs in the first weeks of life and, with one exception, all died of a cardiac cause.

Major cardiovascular malformations were found in all 10 cases. Four had, in association with a ventricular septal defect of the infundibular type, an interrupted aortic arch, which was left-sided in two and right-sided in two other cases. Four patients had truncus arteriosus type I, in two of them associated with a right-sided aortic arch. Two patients with tetralogy of Fallot had a right-sided aortic arch. Only two of the 10 had a normally developed left aortic arch. Aberrant subclavian arteries were found in five cases.

From our observations and a survey of the previously published patients it appears that 90 per cent of the necropsy-proven cases of DiGeorge syndrome have cardiovascular malformations and that 95 per cent of these malformations can be classified as aortic arch anomalies, truncus arteriosus, or tetralogy of Fallot.

Thymic aplasia or hypoplasia is often associated with complete or partial absence of the parathyroid glands and almost invariably with cardiovascular malformations. As both the thymus and parathyroid glands are derivatives of the same embryonic structures, this developmental anomaly has been called the III-IV pharyngeal pouch syndrome.[1 2] DiGeorge[3] described the clinical syndrome characterised by neonatal hypocalcaemia and defective thymus-dependent cellular immunity in infancy in which the most common cause of death is severe cardiac malformation usually involving the aortic arch or conotruncus.

Our recent experience with 10 patients who died within the first year of life and came to necropsy indicates that this syndrome is not as rare as generally thought. This paper deals with the cardiovascular findings and reviews the published reports.

Subjects

In a consecutive series of 510 paediatric necropsies performed at the University Hospital Gasthuisberg over a three-year period, the anatomy of the thymus was carefully examined as a routine. Ten patients with agenesis or hypoplasia of the thymus were found. Stress involution was differentiated from hypoplasia on the basis of the symmetrical aspect of the shrinkage and the persistence of the normal bilobed anatomy. In hypoplasia at least one lobe of the thymus is completely absent. Thymic aplasia was defined as the absence of thymic tissue in the upper mediastinum. In nine of the 10 patients the tissue of the anterosuperior mediastinum and neck, which had been removed en bloc, was serially sectioned at 5 μ and every 10th section was stained and histologically examined. All 10 patients had presented to the departments of paediatric cardiology or neonatology with cardiac symptoms and signs. Ventricular septal defects were classified after Goor and Lillehei[4] and truncus arteriosus after Collett and Edwards.[5] Two types of interrupted aortic arch[6] were distinguished: interruption distal to the left subclavian artery (type A) and interruption distal to the left common carotid artery (type B). This terminology was also applied,

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mutatis mutandis, when a right-sided aortic arch was interrupted.

Results

(1) CLINICAL OBSERVATIONS

The relevant clinical data are summarised in Table 1. The sex predilection was predominantly male: seven male to three female. Maternal ages ranged between 22 and 39 years. Pregnancies lasted between 34 and 40 weeks and birthweight ranged between 1·1 and 3·8 kg. In five cases pregnancy had been unremarkable. Pre-eclampsia had been noted in one case (case 2). In one mother (case 5) with a nodular goitre, thyroxin had been discontinued but thyroid function remained normal throughout pregnancy. Because of hydramnios a caesarean section was performed at 34 weeks of gestation. At birth the child had a goitre. Hydramnios was also a complication in two other pregnancies (cases 6 and 9). One mother (case 7 had had a febrile illness in the first trimester of pregnancy.

In all patients congestive heart failure or cyanosis were the presenting features which led to hospital admission. Only one infant (case 1) had severe hypocalcaemia and overt tetany. In one other patient (case 3) borderline hypocalcaemia (8·1 mg/100 ml) did not produce neurological symptoms. The serum calcium level was normal in six of the eight cases in which it was determined. Bronchopneumonia was a complication in three patients (cases 2, 3, and 8) and oral moniliasis and gastroenteritis in one patient (case 8).

Cranofacial stigmata (Table 2) were noted in six patients. The most common were low-set ears, hypertelorism, and retrognathia (Fig. 1). The fairly specific "fish-mouth" appearance was observed in four cases. In one of them (case 3) this facial expression was enhanced by ankylosis of the mandibular joint.

Table 2 *Craniofacial stigmata*

Case no.	*Craniofacial stigmata*
1	Low-set ears, retrognathia, high-arched palate
3	Hypertelorism, retrognathia, ankylosis of the mandibular joint, fish-mouth
6	Hypertelorism, low-set ears, retrognathia
7	Low-set ears, short philtrum, retrognathia, and high-arched palate, fish-mouth
8	Low-set ears, hypertelorism, retrognathia, fish-mouth
9	Slightly deformed ears, short philtrum, retrognathia, fish-mouth

Death occurred within the first month of life in seven patients. Two patients died at 3 months. The longest survivor and only patient who was operated upon (case 7) died in a low cardiac output state three days after total correction of truncus arteriosus.

(2) PATHOLOGICAL FINDINGS

Cardiovascular anomalies (Table 3, Fig. 2)
All hearts were situated on the left side and presented with visceroatrial situs solitus and concordant atrioventricular connections.

Major aortic arch anomalies were encountered in four patients (Fig. 3). Two patients had an interrupted left aortic arch, type A in one and type B in the other. In two cases an interrupted right aortic arch type B was observed. All four patients had an infundibular ventricular septal defect. In one of them (case 2) a distinct shift of the crista supraventricularis to the left produced narrowing of the subaortic region above the ventricular septal defect (Fig. 4). In three patients (cases 4, 5, and 10) the aortic valve was bicuspid but not difinitely narrowed.

Six children had conotruncal anomalies. Truncus arteriosus type I was found in four children, in

Table 1 *Clinical data in 10 patients with DiGeorge syndrome*

Case no.	*Sex*	*Maternal age (y)*	*Gestation (wk)*	*Birthweight (g)*	*Hypocalcaemia*	*Age at death*	*Cause of death*
1	M	22	36	2370	Severe	3 months	Cardiac failure
2	M	39	37	2600	No	8 days	Cardiac failure
3	M	24	40	3300	Slight	5 days	Cardiac failure
4	F	26	40	2800	ND	12 days	Cardiac failure
5	M	29	34	2290	No	4 hours	Postnatal anoxaemia
6	M	21	34	1100	ND	2 days	Cardiac failure, intravascular coagulation
7	M	28	38	2320	No	1 year	Postoperative death
8	F	29	40	3050	No	3 months	Cardiac failure
9	M	28	36	2900	No	1 month	Cardiac failure
10	F	22	40	3800	No	16 days	Cardiac failure

ND, calcaemia not determined.

two of them associated with a right aortic arch. The two patients with tetralogy of Fallot also had a right aortic arch. In one of them (case 6) agenesis of the pulmonary valve and aneurysmal dilatation of the main pulmonary artery were observed. At the site of the pulmonary valve only a fringe of nodular and dysplastic tissue was found. The ductus arteriosus was absent.

Anomalies of the subclavian arteries (Fig. 2) were common. Four patients had an aberrant left subclavian artery and one patient had an aberrant right subclavian artery. In one case with bilateral ductus arteriosus (case 10) the left subclavian artery was isolated from the aortic arch. It connected with the pulmonary artery via a left ductus arteriosus. The right ductus arteriosus supplied the descending aorta. Other cardiovascular findings were: bicuspid aortic valve (cases 4, 5, and 10), bicuspid pulmonary valve (case 4), and bilateral superior vena cava (case 3). Pulmonary venous connection was normal in all patients and in all the foramen ovale was patent, with an incompetent valve in three (cases 3, 4, and 6).

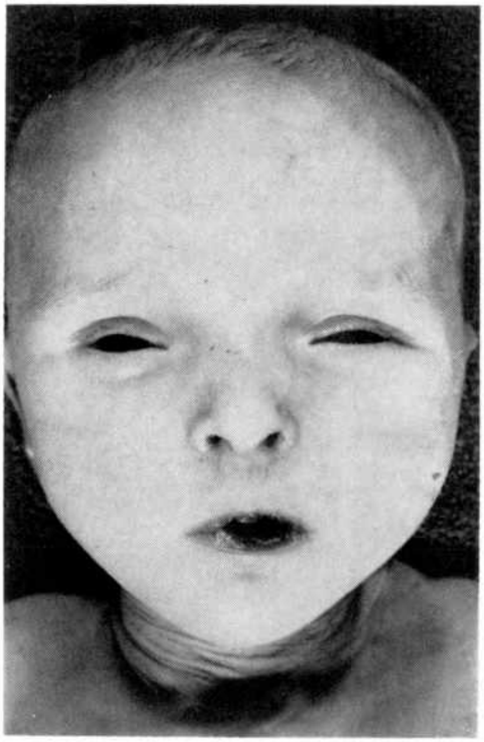

Fig. 1 *Facies (case 8) characterised by low-set ears, hypertelorism, retrognathia, and fish-mouth appearance.*

Thymus, lymph nodes, and spleen (Table 3)
In five patients (cases 1, 2, 7, 8, and 10) rudimentary fragments of the thymus could be identified macroscopically. They were derived from the right lobe and were usually ectopic. The left lobe was absent in all cases (Fig. 5). Serial histological examination of the cervical and mediastinal tissue showed small thymic remnants in three other patients (cases 4, 5, and 6). The histological structure of this thymic tissue was normal. Evidence of involution was slight to moderate. No thymic tissue could be found in the remaining two patients (cases 3 and 9).

Compared with the histological structure of the lymph nodes in children of the same age group, the lymph nodes in these 10 patients showed hypocellularity of the paracortical area. The degree of lymphoid depletion of the thymus-dependent zones, however, was variable, even in the same patient. The cortical zone of the lymph nodes was normal with primary and sometimes secondary follicles (cases 1 and 7).

Hypoplasia of the spleen was most striking in case 6, a dysmature infant. The spleen was also abnormally small in the patients with no thymus (cases 3 and 9). In all patients a pronounced hypocellularity of the periarteriolar lymphocytic

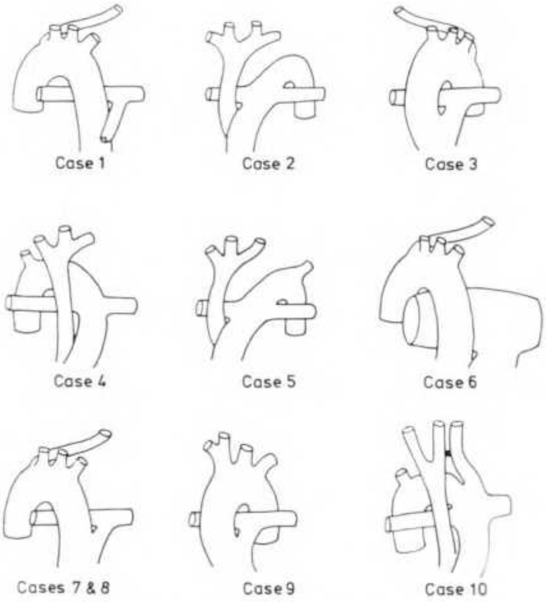

Fig. 2 *Schematic representation of the great arteries arising from the heart in 10 patients with DiGeorge syndrome.*

Table 3 *Pathological findings*

Case no.	*Thymus**	*Parathyroids*	*Spleen**	*Cardiovascular system*
1	1·0 g, absence of left lobe	Absent	15·3 g	Extreme TF, R aortic arch, aberrant L subclavian artery
2	2·2 g, absence of left lobe	3 normal glands	8·3 g	Int L aortic arch type A, inf VSD, L shift of CSV
3	Absent	Absent	3·8 g	Truncus type I, inf VSD, aberrant R subclavian artery, absent DA, bilateral SVC
4	Small nodule (0·7 cm diameter) in R upper mediastinum	Not examined	11·2 g	Int R aortic arch type B, inf VSD, bicuspid aortic valve
5	Small nodule (0·6 × 0·3 × 0·3 cm) deep in R mediastinum	Absent	7·9 g	Int L aortic arch type B, inf VSD, bicuspid aortic and pulmonary valve
6	Small nodule (0·5 cm diameter) in R upper mediastinum	1 hypoplastic gland	2·5 g	TF, absent pulmonary valve, R aortic arch, aberrant L subclavian artery, absent DA
7	0·5 g, small nodule under R thyroid lobe	1 normal gland	23·0 g	Truncus type I, inf VSD, R aortic arch, aberrant L subclavian artery, absent DA
8	0·8 g, absence of left lobe	2 normal glands	5·6 g	Truncus type I, inf VSD, R aortic arch, aberrant L subclavian artery, absent DA
9	Absent	2 normal glands	6·2 g	Truncus type I, inf VSD, absent DA
10	0·4 g, small nodule along R carotid artery	2 normal glands	5·9 g	Int R aortic arch type B, inf VSD, bicuspid aortic valve, bilateral DA

*weight in grams.

CSV, crista supraventricularis; DA, ductus arteriosus; inf, infundibular; int, interrupted; L, left; R right; SVC, superior vena cava; TF, tetralogy of Fallot; truncus, truncus arteriosus; VSD, ventricular septal defect.

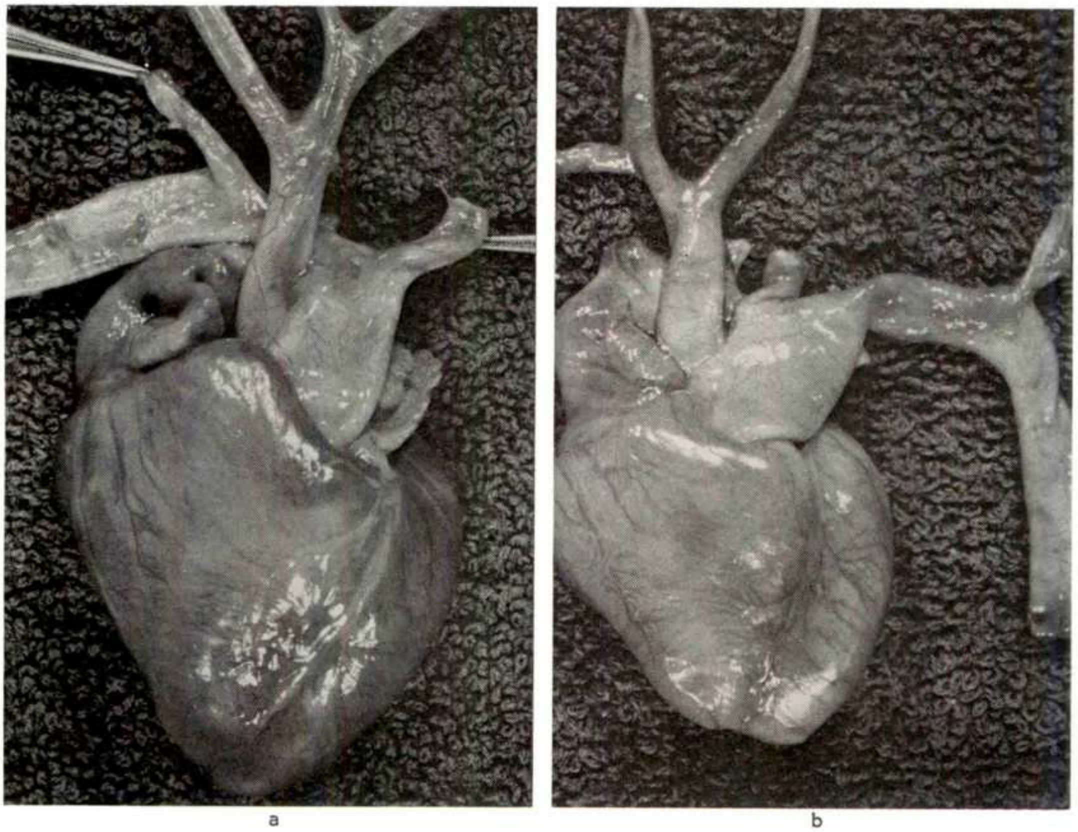

Fig. 3 *Interrupted aortic arch.* (a) *Type B interruption, between the right common carotid artery and the right subclavian artery, in a patient with right aortic arch (case 4). A large ductus arteriosus connects the pulmonary artery with the descending aorta and the right subclavian artery.* (b) *Type B interruption, between the left common carotid artery and the left subclavian artery, in a patient with left aortic arch (case 5).*

sheets was observed. In one patient (case 7) germinal centres in the white pulp were noted.

Thyroid and parathyroids

No gross abnormalities of the thyroid glands were seen. In one patient (case 3) the isthmus was absent. In the patient with congenital goitre (case 5) histological examination showed empty follicles, devoid of colloid and bordered by high-cylindrical cells. The histological structure of the thyroid gland was normal in the others. Even after serial sectioning and histological examination of the anterior mediastinum and neck, which was done in nine of the 10 patients, no parathyroid tissue could be found in three cases (cases 1, 3, and 5). In one patient (case 6) one hypoplastic parathyroid gland was found at the upper pole of the right thyroid lobe. In the other patients, one (case 7), two (cases 8, 9, and 10) or three (case 2) normal parathyroids were found. When present these glands showed a normal histological structure.

ADDITIONAL FINDINGS

One patient (case 1) had hammer toes and bilateral clinodactyly of the 5th finger. Microscopical examination of the right kidney in this patient showed small cartilaginous islands, with absence of cystic structures. The left umbilical artery was

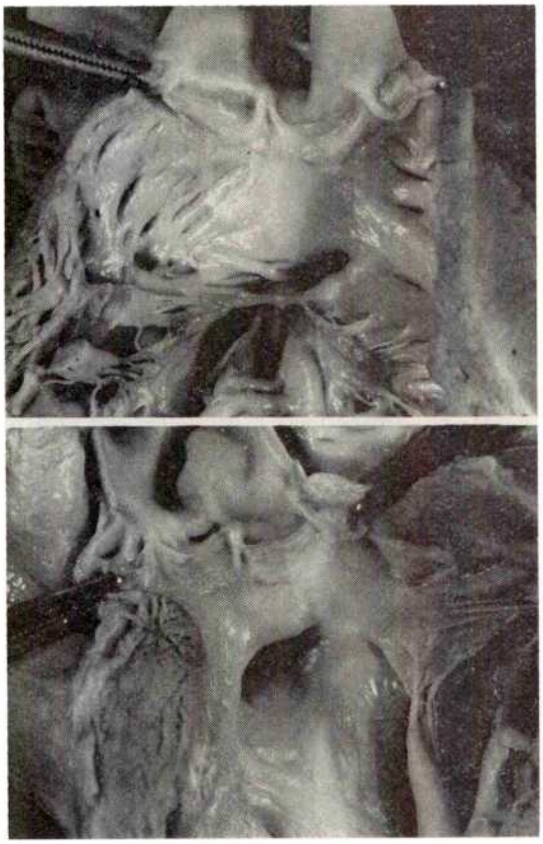

Fig. 4 *Ventricular septal defect in a patient with interrupted left aortic arch (case 2).* Upper panel: *in the opened right ventricle an oval-shaped ventricular septal defect is seen in an unusual location between the conus septum and the sinus septum.* Lower panel: *the left ventricular view. A muscular band below the aortic valve produces narrowing of the left ventricular outflow tract above the ventricular septal defect. It is probably the result of a leftward shift of the crista supraventricularis (see text).*

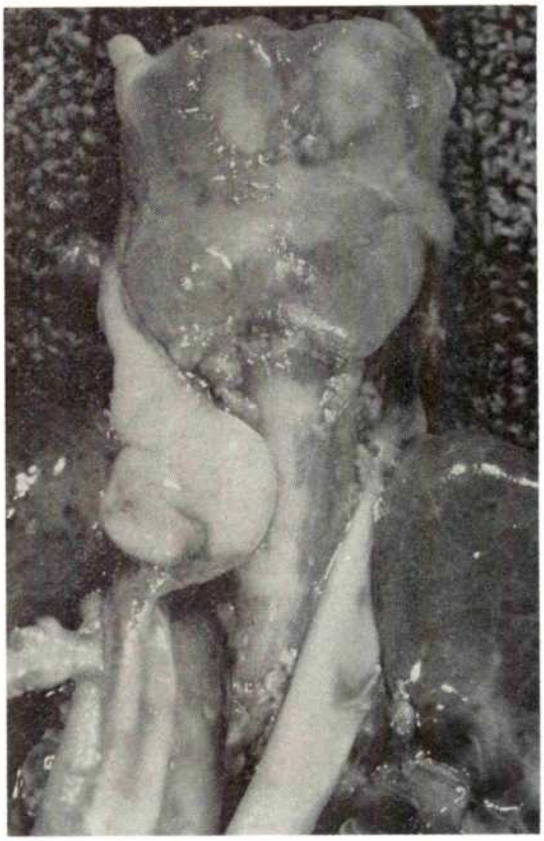

Fig. 5 *Typical aspect of upper mediastinum at necropsy (case 7). The left lobe of the thymus is absent. A small shrimp-shaped nodule of thymic tissue is seen below the right thyroid lobe.*

absent in one patient (case 5). An abnormal lobulation of the right lung was found in seven patients: in three patients only two lobes were present, whereas in the remaining four patients the upper and median lobes were incompletely separated.

Discussion

Congenital absence of the thymus and parathyroid glands has, for many years, been known to be a cause of neonatal hypocalcaemia and tetany.[7] The association with cardiovascular malformations was first noted by Lobdell[8] and by Farber and Vawter.[9] DiGeorge[3] described the clinical spectrum and emphasised the deficit of thymic-dependent immunity. Though the anomaly has been reported as the III-IV pharyngeal pouch syndrome,[1 10] the term DiGeorge syndrome is now widely used. A critical review of the terminology and a classification have been presented by Lischner.[11]

Approximately 50 cases of the DiGeorge syndrome have been reported. The largest series[1] comprises 10 cases but only three with pathological proof. A detailed description of the clinical and necropsy findings in six patients has been presented by Robinson[2] who also reviewed the 26 cases reported before his study. To this number should be added two patients reported by Rose *et al.*,[12] four cases reported by Griscelli and Diebold,[13] two cases described by Shepard *et al.*,[14] and three described by Cintado Bueno *et al.*[15]

In view of the rarity of this syndrome we were surprised to find 10 patients coming to necropsy within a period of three years. This may partly be explained by the fact that the pathologist, alerted by the first case, paid particular attention to the development of the thymus and parathyroid glands in paediatric necropsies, particularly in patients who had congenital heart disease.

All patients presented with cardiac symptoms or signs in the first months of life and, with one exception, all died from a cardiac cause. Only one infant had overt tetany, one had borderline asymptomatic hypocalcaemia, whereas six of the eight patients in whom it was determined had normal serum calcium levels. Our findings are therefore at variance with most previous reports in which tetany or hypocalcaemia were often the major disturbance. They confirm, however, the observations of Cameron[16] who found no signs of hypoparathyroidism in a series of 10 cases. These discrepancies may be explained by the variable pathological composition of the syndrome. Careful macroscopical and serial microscopical examination of the neck and anterior mediastinum performed in nine of our 10 cases, disclosed that in five patients at least one normal parathyroid gland was present. In one other patient one hypoplastic gland was found. Because of the unusual sites of ectopic tissue it is impossible to be certain that the remaining three patients did indeed have "aplasia" of the parathyroid glands. Farber and Vawter[9] found parathyroid tissue high in the submucosa of the posterior pharynx and mentioned that ectopic tissue might also be located along the neural structures of the neck. While it is true that profound hypocalcaemia should alert the clinician to the possibility of DiGeorge syndrome, our experience indicates that this sign may be completely lacking.

Defective cell-mediated immunity did not lead to serious clinical complications in the present series. However, no specific studies of immune function were performed, which might have disclosed an abnormally low percentage of thymus-dependent lymphocytes (T-lymphocytes) or depression in antibody response to specific immunisation.[11 17] A review of the previously reported children with an immunological deficit[1] shows that they were older than our patients and that most of them had less severe heart disease. We presume therefore that the severity of the cardiac condition in our patients caused early death before immunological problems could arise. It should also be stressed that in many patients part of the thymus or ectopic thymic tissue may be found.[2] In three of our patients a hypoplastic right lobe (weighing 0·8 g, 1·0 g, and 2·25 g) was present. In five other patients serial microscopical examination disclosed the presence of nodules of ectopic thymic tissue. Only two patients could, within the limits of careful post-mortem examination, be considered to be "athymic". The variability of the pathological findings and the corresponding degree of deficiency of the cell-mediated immunity, led Lischner[11] to propose a classification in which partial and complete forms of the DiGeorge syndrome are distinguished.

As commented on in previous studies[1 2] some patients have a peculiar facies characterised by hypertelorism, low-set ears, a short philtrum, and retrognathia. A fish-mouth appearance was noted in four of our patients.

Various other anomalies have been reported in this syndrome, which, however, are neither constant nor characteristic: severe thyroid hypoplasia,[2 8 18] oesophageal atresia,[3 18] choanal atresia,[18] hydronephrosis,[1] and renal glomerular and tubular microcysts.[2] It is noteworthy that seven of 10 patients in the present study had an abnormal lobulation of the right lung. This high incidence has not been reported before.

Major cardiovascular malformations (Table 3) were observed in all 10 cases. Four patients had, in association with an infundibular septal defect, an interrupted aortic arch which was left-sided in two and right-sided in the other two. In one patient a leftward displacement of the crista supraventricularis produced narrowing of the subaortic region. The three other patients had a bicuspid aortic valve. Thus, in all four hearts a structure in the left ventricular outflow tract was found which, in fetal life, could have reduced forward aortic flow and impeded normal growth of the aortic arch. Identical observations in larger series of patients with interrupted aortic arch have been made by Van Praagh *et al.*[19] and Moulaert.[20] Four patients had truncus arteriosus type I and two had tetralogy of Fallot. Both these anomalies can be considered to be conotruncal malformations. Out of 10 patients only two (cases 3 and 9) had a normal left aortic arch. In two patients a left aortic arch was interrupted and in the remaining six the aortic arch was right-sided. Equally common were anomalies of the subclavian arteries, which were noted in six cases. Agenesis of the pulmonary valve and aneurysmal dilatation of the main pulmonary artery encountered in one of our patients with tetralogy of Fallot (case 6) have previously been described in two other patients with DiGeorge syndrome.[12] The association has also been briefly mentioned by Cameron.[16]

Compiling the 26 cases reported or reviewed by Robinson,[2] those reported by Rose *et al.*,[12] Shepard *et al.*, [14] Griscelli and Diebold,[13] Cintado Bueno *et al.*, [15] and the 10 patients of the present study, a total number of 52 well-documented cases are available for further analysis. Only seven out of 52 patients had normal cardiovascular findings. The cardiovascular malformations encountered in 45 patients are listed in Table 4. Right aortic arch, without associated anomalies, was observed in seven patients (16%), double aortic arch in two (0·44%), and interrupted aortic arch in eight cases (18%). Twelve patients (27%) had truncus arteriosus and 13 (29%) had tetralogy of Fallot. A very high incidence (19 cases, 42%) of right aortic arch was noted in the combined series: it occurred as an isolated anomaly in seven patients, in association with tetralogy of Fallot in seven, and with truncus arteriosus in three. In two patients in the present series (cases 4 and 10) a right-sided aortic arch was interrupted. There was no correlation between the type of the cardiovascular malformation and the degree of hypoplasia of the thymus and parathyroids.

The following conclusions can be reached: (1) cardiovascular malformations are found in approximately 90 per cent of the necropsy-proven cases of DiGeorge syndrome, (2) the vast majority can be classified as aortic arch anomalies (right aortic arch, interrupted aortic arch, aberrant subclavian artery) and/or conotruncal anomalies (tetralogy of Fallot and truncus arteriosus). Together these rather uncommon types of malformation account for 95 per cent of all forms of congenital heart disease observed in this syndrome, (3) conversely, common types of congenital heart disease, such as isolated ventricular or atrial septal defect, coarctation of the aorta, and aortic stenosis have, to the best of our knowledge, not been reported.

The concurrence of malformations of the thymus and parathyroid glands can easily be explained by their embryogenesis, as the thymus originates from the third pharyngeal pouch and the parathyroid glands are derivatives of both the third and fourth pharyngeal pouches. The frequent association with relatively rare forms of congenital heart disease is intriguing and so far unexplained. Harvey *et al.*[10] drew attention to the close proximity of the aortic arch and the third and fourth pharyngeal pouches during fetal life and postulated some sort of damage in this area at approximately four weeks' gestation. Robinson[2] proposed an ingenious mechanism of pathogenesis in which the conotruncal anomaly would be the primary event,

Table 4 *Cardiovascular malformations in 45 patients with DiGeorge syndrome*

Malformations	*Reported cases**	*Present study*	*Combined series*
R aortic arch	7		7
Double aortic arch	2		2
Interrupted aortic arch			8
L aortic arch	4	2	6
R aortic arch		2	2
Truncus arteriosus			12
with L aortic arch	7	2	9
with R aortic arch	1	2	3
Tetralogy of Fallot			13
with L aortic arch	5		5
with R aortic arch	4	1	5
with L aortic arch and PV agenesis	1		1
with R aortic arch and PV agenesis	1	1	2
Transposition of great arteries	1		1
Pulmonary stenosis	1		1
Persistent ductus arteriosus (large)	1		1
Totals	35	10	45

* In this series the 26 cases with cardiovascular malformations reported or reviewed by Robinson[2] were included. Also included were two cases reported by Rose *et al.*,[12] one case reported by Shepard *et al.*,[14] three cases reported by Griscelli and Diebold,[13] and three cases reviewed by Cintado Bueno *et al.*[15]
R, right; L, left; PV, pulmonary valve.

leading to altered perfusion of the left fourth aortic arch and its frequent deletion (interrupted aortic arch, right aortic arch). He further postulated the premature involution of the thyroidea ima artery which is the main embryonic blood supply of the third and fourth pharyngeal pouches. This hypothesis, however, has not been corroborated by pathological or embryological findings.

The DiGeorge syndrome does not seem to be genetically determined. A familial incidence has been reported rarely.[14 21] Males are more frequently affected than females with a sex ratio of approximately 2:1. No teratogenic agent has been incriminated so far.

We wish to thank Dr Richard Van Praagh and Dr André Moulaert for their criticism and valuable advice.

References

1 Freedom RM, Rosen FS, Nadas AS. Congenital cardiovascular disease and anomalies of the third and fourth pharyngeal pouch. *Circulation* 1972; **46:** 165–72.
2 Robinson HB Jr. DiGeorge's or the III-IV pharyngeal pouch syndrome. Pathology and a theory of pathogenesis. *Perspect Pediatr Pathol* 1975; **2:** 173–206.
3 DiGeorge AM. Discussions on a new concept of the cellular basis of immunity. *J Pediatr* 1965; **67:** 907–8.
4 Goor D, Lillehei CW. *Congenital malformations of the heart.* New York: Grune & Stratton, 1975.
5 Collett RW, Edwards JE. Persistent truncus arteriosus: a classification according to anatomic types. *Surg Clin North Am* 1949; **29:** 1245–70.
6 Celoria G, Patton R. Congenital absence of the aortic arch. *Am Heart J* 1959; **58:** 407–13.
7 Rössle R. Ueber gleichzeitige Missbildungen der branchiogenen Organe und über angeborenen Mangel der Epithelkörperchen. *Virchows Arch Pathol Anat* 1932; **283:** 41–57.
8 Lobdell DH. Congenital absence of the parathyroid glands. *Arch Pathol* 1959; **67:** 412–5.
9 Farber S, Vawter G, eds. Clinical pathological conference, Children's Medical Center, Boston, Mass. *J Pediatr* 1960; **56:** 690–7.
10 Harvey JC, Duncan WT, Elders MJ, Hughes ER. Third and fourth pharyngeal pouch syndrome, associated vascular anomalies and hypocalcemic seizures. *Clin Pediatr* 1970; **9:** 496–9.
11 Lischner H. DiGeorge syndrome(s). *J Pediatr* 1972; **81:** 1042–4.
12 Rose JS, Levin DC, Goldstein S, Laster W. Congenital absence of the pulmonary valve associated with congenital aplasia of the thymus (DiGeorge's syndrome). *Am J Roentgenol* 1974; **122:** 97–102.
13 Griscelli C, Diebold N. Le syndrome de DiGeorge. A propos de quatre nouvelles observations. *Journées Parisiennes de Pédiatrie* 1976; 171–86.
14 Shepard MK, Linman SK, Cavazos A. Familial thymic aplasia with intrauterine growth retardation and fetal death: a new syndrome or a variant of DiGeorge syndrome. *Birth Defects* 1976; **12:** 123–5.
15 Cintado Bueno C, Ariza Almeida S, Castillo Camacho JA, Atienza Contreras A, Toro Ortega J. Sindrome de DiGiorge. Estudo cardiologico en tres casos. *An Esp Pediatr* 1977; **10:** 532–42.
16 Cameron A. Malformations of the thymus and cardiovascular system (abstract). *Arch Dis Child* 1965; **40:** 334.
17 Gatti RA, Gershanik JJ, Levkoff AH, Wertelecki W, Good RA. DiGeorge syndrome associated with combined immonodeficiency. *J Pediatr* 1972; **81:** 920–6.
18 Dische MR. Lymphoid tissue and associated congenital malformations in thymic agenesis. *Arch Pathol* 1968; **86:** 312–6.
19 Van Praagh R, Bernhard W, Rosenthal A, Parisi L, Fyler DC. Interrupted aortic arch. Surgical treatment. *Am J Cardiol* 1971; **27:** 200–11.
20 Moulaert A. *Ventricular septal defects and anomalies of the aortic arch.* Leiden: Thesis, University of Leiden, 1974.
21 Steele RW, Limas C, Thurman GB, Schuelein M, Bauer H, Bellanti JA. Familial thymic aplasia. Attempted reconstitution with fetal thymus in a millipore diffusion chamber. *N Engl J Med* 1972; **287:** 787–91.

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Case reports

Br Heart J 1980; **44:** 460–3

Coronary artery steal via large coronary artery to bronchial artery anastomosis successfully treated by operation

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SUMMARY We report a patient with a large coronary artery to bronchial artery anastomosis causing angina by coronary steal. Angina was refractory to medical treatment, but successfully relieved by surgical ligation of the anastomosis.

Extracardiac coronary anastomoses are rare and have received little attention since the initial necropsy description in 1803.[1] Since the introduction of angiography small anastomoses have been shown between the coronary and bronchial arterial circulations in normal subjects,[2] which have little, if any, haemodynamic significance. We report a patient with a large coronary artery to bronchial artery anastomosis and bronchiectasis in whom shunting of blood from the coronary circulation resulted in angina, that is, a coronary steal syndrome. His angina was refractory to medical treatment but was relieved by surgical ligation of the anastomosis and resection of the bronchiectatic left lower lobe.

Case history

A 56-year-old man was admitted for investigation of recurrent severe angina pectoris which had been present for one year; in addition, there had been two episodes of prolonged chest pain occurring at rest and associated with sweating. He gave a history of spontaneous pneumothorax resulting from a ruptured emphysematous bulla, and for 15 years he had suffered from bronchial asthma which was treated with bronchodilators.

Examination of the cardiovascular system was normal. Respiratory excursion was reduced, and there was an inspiratory and expiratory wheeze over the middle and lower zones on both sides, and crackles over the left lower and middle zones.

Examination of the cardiovascular system was normal. Respiratory excursion was reduced, and there was an inspiratory and expiratory wheeze over the middle and lower zones on both sides, and crackles over the left lower and middle zones.

Electrocardiogram showed sinus rhythm, a normal QRS vector, and flat T waves in leads III, aVF, and V5–6. During the exercise electrocardiogram, a heart rate of 146 beats per minute was attained, but there were no further electrocardiographic abnormalities. Chest radiograph showed displacement of the heart and mediastinum to the left, elevation of the left hemidiaphragm, and thin-walled ring shadows anteriorly in the left zones consistent with emphysematous bullae.

Pulmonary function tests showed moderately severe obstructive airways disease, partially reversible with bronchodilators. Bronchography showed severe bronchiectasis of all the basal segments of the left lower lobe.

Cardiac catheterisation showed no haemodynamic abnormalities, but coronary arteriography demonstrated a very large and tortuous vessel arising from the proximal left circumflex coronary artery (Fig. 1), which passed posteriorly over the left atrium into the lower part of the left lung where numerous small vessels were seen to fill. The remaining left coronary artery and the right coronary artery were entirely normal. Left ventriculogram showed good function except for an area of hypokinesis apico-inferiorly. Pulmonary angiogram showed that the left lower lobe pulmonary artery did not opacify, but the remaining pulmonary vasculature was normal.

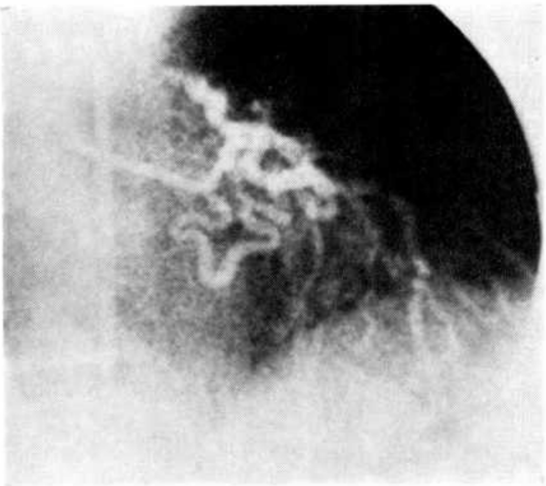

Fig. 1 *Left coronary arteriogram showing filling of a large tortuous anastomotic vessel taking origin from the circumflex artery and passing posteriorly to the left lower lobe of the lung. The remaining circumflex and anterior descending coronary arteries are normal.*

MANAGEMENT

Before investigation by coronary arteriography the patient's angina was treated with glyceryl trinitrate initially, but this resulted in intolerable headaches. Subsequent treatment with a series of selective beta-adrenergic blocking agents resulted in some symptomatic benefit, but exacerbation of his bronchial asthma to a degree which necessitated hospital admission and reduction in dosage. After demonstration of the coronary to bronchial artery anastomosis without coronary narrowing, it was assumed that his angina was the result of a coronary steal syndrome. As he continued to have episodes of severe chest pain, he was submitted to left thoracotomy and ligation of the anastomotic vessel, together with excision of a severely bronchiectatic left lower lobe. This resulted in complete relief of symptoms which have not recurred over a three-year follow-up period.

Discussion

Anastomoses between the coronary arteries and bronchial arteries have been shown at necropsy[1] and at cardiac catheterisation in approximately 25 per cent of normal subjects.[2 3] These anastomoses are small, of little or no haemodynamic importance, and have been regarded as congenital in origin. By contrast, large anastomoses occur in pulmonary atresia,[4] tetralogy of Fallot,[5] supravalvar aortic stenosis,[6] and coronary artery disease,[7] by way of which large quantities of blood may be shunted to or from the coronary and bronchial arterial circulations. Hitherto only one case has been reported in which such an anastomosis resulted in symptoms.[8] In this patient paroxysmal atrial fibrillation developed because of coronary steal from the sinuatrial artery via an anastomosis which was thought to have rendered the sinuatrial node ischaemic.[8] Our patient was also symptomatic with severe angina of one year duration.

The reason for these small congenital anastomoses becoming functional is not known, but it has been suggested[8] that a pressure difference between the coronary and bronchial arterial circulations may result in their enlargement and, therefore, their becoming haemodynamically important. Support for this suggestion is provided indirectly in several circumstances. Shunting of blood from the coronary to the bronchial arteries, or coronary steal, occurs either when coronary artery pressure increases relative to bronchial artery pressure as in supravalvar aortic stenosis,[6] or when bronchial artery pressure decreases relative to coronary artery pressure as in pulmonary atresia,[4] and tetralogy of Fallot.[5] The reduction in bronchial artery pressure in these conditions is the result of filling of large capacitance, low flow, and low pressure pulmonary arteries from the bronchial arteries. Shunting of blood in the reverse direction, or bronchial steal, has been demonstrated in patients with proximal stenoses of the coronary arteries[7] in whom distal coronary artery pressure is reduced compared with bronchial artery pressure. In addition, in patients with proximal coronary artery stenoses not only is the incidence of anastomoses significantly greater than normal, but a correlation has been demonstrated between the severity of coronary stenosis and the size of the anastomoses.[7]

Our patient had bronchiectasis, and in this condition anastomoses develop between the bronchial and the pulmonary arteries at the level of the third to sixth order bronchi, and also more distally in relation to systemic vessel proliferation in the walls of bronchiectatic sacs and destroyed lung tissue.[9 10] The increased bronchial arterial blood flow and large proximal bronchial to pulmonary anastomoses permit retrograde filling of the pulmonary arteries which would account for the failure of the left lower lobe pulmonary artery to opacify in our patient's pulmonary arteriogram. This lowering of bronchial arterial pressure relative to coronary arterial pressure in our patient may have led to the gross enlargement of an originally small congenital coronary to bronchial anastomosis.

Anastomoses between the coronary and bronchial arteries have similar morphology regardless of the direction of blood flow.[3] These vessels are tortuous, of large calibre, and invariably are between the left circumflex coronary artery and the bronchial arteries, because the only point of entry to the heart is via the pericardial reflection posterior to the heart, to which the bronchial arteries are closely anatomically related. The only other possible site of coronary to bronchial anastomoses is via transpericardial vascularisation, which only occurs when the visceral and parietal pericardium are adherent after pericarditis. Coronary arteriography in our patient showed just such a large tortuous vessel taking origin from the left circumflex artery, shunting blood to the bronchial arteries. This anastomosis had presumably caused angina by a coronary steal which had deprived the inferior myocardium of blood and also resulted in the area of hypokinesis apico-inferiorly on the left ventriculogram.

References

[1] Von Haller A. *Physiology*. Troy, Ohio: Penniman, 1803: 35.

[2] Björk L. Anastomoses between the coronary and bronchial arteries. *Acta Radiol (Diagn) (Stockh)* 1966; **4:** 93–6.

[3] Moberg A. Anastomoses between extracardiac vessels and the coronary arteries. *Acta Med Scand (Suppl)* 1968; **485:** 5–26.

[4] Jefferson K, Rees S, Somerville J. Systemic arterial supply to the lungs in pulmonary atresia and its relation to pulmonary artery development. *Br Heart J* 1972; **34:** 418–27.

[5] Nordenström B. Selective catheterization and angiography of bronchial and mediastinal arteries in man. *Acta Radiol (Diagn) (Stockh)* 1967; **6:** 13–25.

[6] Do Valle PV, Barcia A, Bargboun LM Jr. Angiographic study of supravalvular aortic stenosis and associated lesions. Report of five cases and review of the literature. *Ann Radiol (Paris)* 1969; **12:** 779–96.

[7] Björk L. Angiographic demonstration of extracardiac anastomoses to the coronary arteries. *Radiology* 1966; **87:** 274–7.

[8] Smith SC, Adams DF, Herman MV, Paulin S. Coronary-to-bronchial anastomosis. An *in vivo* demonstration by selective coronary arteriography. *Radiology* 1972; **104:** 289–90.

[9] Liebow AA, Hales MR, Lindskog GE. Enlargement of the bronchial arteries and their anastomoses with the pulmonary arteries in bronchiectasis. *Am J Pathol* 1949; **25:** 211–31.

[10] Turner-Warwick M. Pre-capillary systemic-pulmonary anastomoses. *Thorax* 1963; **18:** 225–37.

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Addendum

Since describing the above patient with a coronary artery to bronchial artery anastomosis we have investigated another patient with a similar anatomical abnormality. This 44-year-old man was admitted for investigation of recurrent praecordial

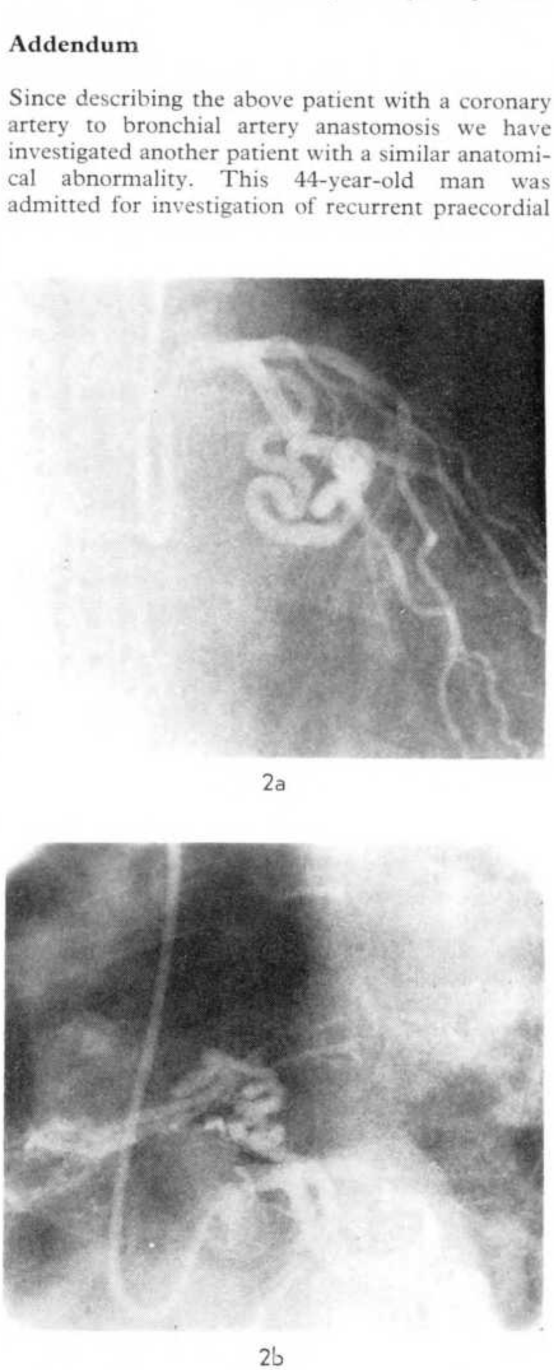
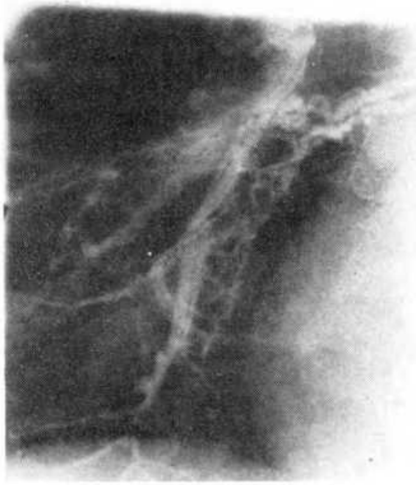


Fig. 2 *A large tortuous artery is shown arising from the left circumflex coronary artery* (a) *which passes posteriorly* (b) *to anastomose with bronchial arteries which in turn anastomose with the right middle and lower lobe pulmonary artery* (c).

pain unrelated to exertion. Clinical examination, electrocardiogram, and chest radiograph were normal. Coronary arteriography performed to exclude coronary artery disease as a cause for the chest pain showed a very large tortuous artery arising from the left circumflex coronary artery. This vessel passed posteriorly into the mediastinum where it anastomosed with a leash of small, presumably bronchial, arteries; these in turn anastomosed with branches of the right middle and lower lobe pulmonary arteries resulting in opacification of these pulmonary arteries after the injection of contrast medium into the left coronary artery (Fig. 2 a b c). As in the previous patient there was no coronary atheroma in either the right or left coronary arteries. Because of our previous observation of the relation between coronary artery to bronchial artery fistula and bronchiectasis, bilateral bronchograms were performed. These showed moderately severe bronchiectatic changes in the right middle lobe and the apical segment of the right lower lobe. In the absence of a history of angina or severe recurrent respiratory symptoms, operation was not advised but would be reconsidered should these symptoms arise.



2c

Our thanks are due to Dr M Honey for permission to publish details of this case.

Br Heart J 1980; **44:** 464–8

Rupture of pulmonary artery aneurysm associated with persistent ductus arteriosus

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SUMMARY Fatal haemopericardium occurred in a 14-year-old boy after rupture of a pulmonary artery aneurysm. Persistent ductus arteriosus with severe pulmonary hypertension was confirmed by cardiac catheterisation when he was 4 weeks old. Attempted closure of the ductus at 4 years had not been possible because of apparent high pulmonary resistance. Exercise tolerance had been good enough to permit competitive horse riding up to the day of death. Light and electron microscopy showed widespread cystic medionecrosis of the elastic pulmonary arteries.

Case report

This boy was born at term, weighing 3235 g, to a 27-year-old woman. She had been in contact with rubella when two months pregnant. After delivery he was noted to be mildly cyanosed with only the right upper quadrant of the body being pink. During the first day the left upper quadrant also became pink. Initially his general condition was good but within a week feeding had deteriorated. By the age of 10 days there was evidence of heart failure in the form of hepatic enlargement and dyspnoea, but digitalisation, low-sodium diet, and oxygen led to some improvement. At 4 weeks, a pansystolic murmur maximal in the second and third left intercostal spaces was audible with a diastolic component. Chest *x*-ray film showed cardiomegaly and an electrocardiogram suggested right ventricular dominance. Right heart catheterisation at this time (Table) showed severe pulmonary hypertension and biplane cineangiocardiography from the pulmonary trunk showed a persistent ductus arteriosus, though there was no evidence of left-to-right shunt on oximetry (Table). The femoral pulses were barely palpable and retrograde aortography at 6 weeks suggested the possibility of a preductal coarctation, though the proximal to distal pressure drop was minimal (Table). Surgical intervention at this time was considered too risky.

Table *Cardiac catheter data**

	Blood pressure (mmHg) at age			*Oxygen saturation (%) at age*	
	4 wk	*6 wk*	*4 y*	*4 wk*	*4 y*
SVC	—	—	—	64	76·0
HRA	—	—	—	50	64·5
MRA†	5/–2	—	2/–4	44	63·0
LRA	—	—	—	43	61·0
IVC	—	—	—	38	68·0
HRV	—	—	—	44	—
MRV	110/0	—	90/0	54	59·5
Apex RV	—	—	—	44	64·5
MPA	110/40	—	90/60	43	79·0
Aorta:					
proximal	—	80/40	90/65	—	—
subclavian	—	75/40	—	—	—
distal	—	75/40	—	—	80·5

SVC, superior vena cava; HRA, high right atrium; MRA, mid-right atrium; LRA, low right atrium; IVC, inferior vena cava; HRV, high right ventricle; MRV, mid-right ventricle; MPA, main pulmonary artery.

*Performed under sedation and local anaesthesia. No supplementary oxygen administered.

†Only two atrial wave forms discernible because of tachycardia.

During the next four years he had occasional chest infections, but after some delay gained weight and developed normally. He was able to run and play with other children and developed only mild dyspnoea on moderate exercise, but sometimes became cyanosed on crying. At 4 years of age the femoral pulses were easily palpable and there was no clubbing or cyanosis. There was now clinical evidence of cardiomegaly with a displaced apex beat and the sternum could be seen to bulge. A basal pansystolic murmur (grade 4) was accompanied by a thrill and a diastolic murmur (grade 1) was present. The second sound in the pulmonary area was loud but normally split; an electrocardiogram showed right ventricular hypertrophy. At repeat cardiac catheterisation, a catheter was passed from the right ventricle to the pulmonary artery and through the patent ductus into the descending aorta. Pulmonary and systemic pressures were almost equal and oximetry provided evidence of bidirectional shunting (Table).

Although angiocardiography was not repeated, the diagnosis was now considered to be persistent ductus arteriosus with severe pulmonary hypertension, without evidence of coarctation. In view of the poor prognosis without surgery an attempt was made to close the ductus. At thoracotomy the ductus (0·7 cm diameter) was clamped for 20 minutes. During this time the aortic pressure fell by 20 mmHg, the aortic and pulmonary artery pressures remained equal at 105 mmHg, and cyanosis occurred. On release of the clamp the aortic pressure rose to 125 mmHg and tissue oxygenation improved. These findings were considered consistent with a state of probably irreversible high pulmonary resistance and it was thought unreasonable to divide the ductus.

Subsequent development was unremarkable and an electrocardiogram and chest *x*-ray film taken when aged 11 is shown in Fig. 1 and Fig. 2a. At 13 years there was slight cyanosis at rest and an early diastolic murmur suggestive of pulmonary regurgitation. However, there was no effort intolerance and during the year before his death he won 32 cups for showjumping. On the day of his death, aged 14 years 4 months, he won another riding competition without dyspnoea or fatigue, but 20 minutes after his last ride he collapsed and died.

NECROPSY

External examination showed neither clubbing nor stigmata of Marfan's syndrome. The pericardial cavity was tense and distended with 550 ml fresh blood originating from a 4 cm linear tear in the pulmonary artery (Fig. 2b). The tear started 0·5 cm above the pulmonary valve in an area of fusiform aneurysmal thinning 8 cm in length and 12 cm at its maximal circumference.

A persistent ductus arteriosus connected the main pulmonary artery and the descending aorta and measured 0·8 cm in diameter and 1·0 cm in length before fixation. The right and left ventricles were hypertrophied (140 and 310 g, respectively). The remainder of the heart and the aorta appeared normal, with no coarctation.

On light microscopy, the tunica media of the aneurysm contained numerous pools of acid mucopolysaccharide which stained positively with alcian blue and metachromatically with toluidine blue. There was widespread fragmentation (Fig. 2c) and loss of elastic tissue with an increase in collagen fibres. Electron microscopy (Fig. 2d) confirmed these findings and pronounced vacuolisation of the medial smooth muscle cells was observed. Similar but less severe changes were seen in the remainder of the elastic pulmonary arteries, and in the smaller vessels the minimal branching of the elastic fibres suggested a persistence of fetal-type vasculature.

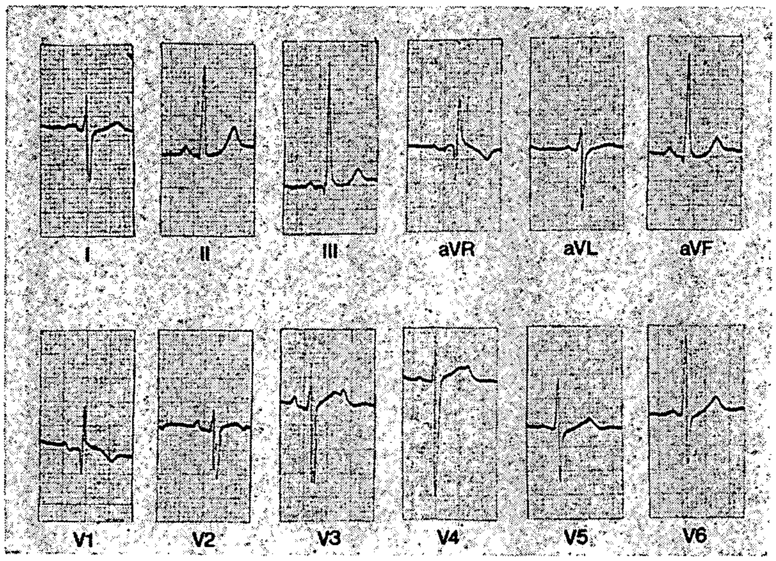
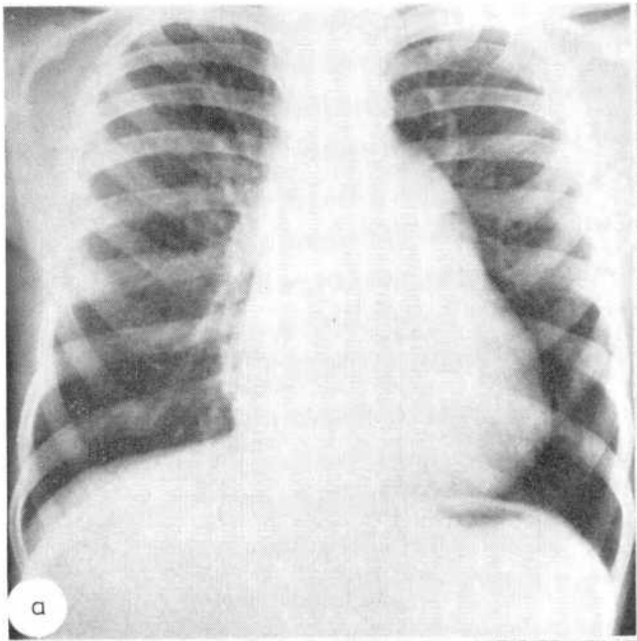
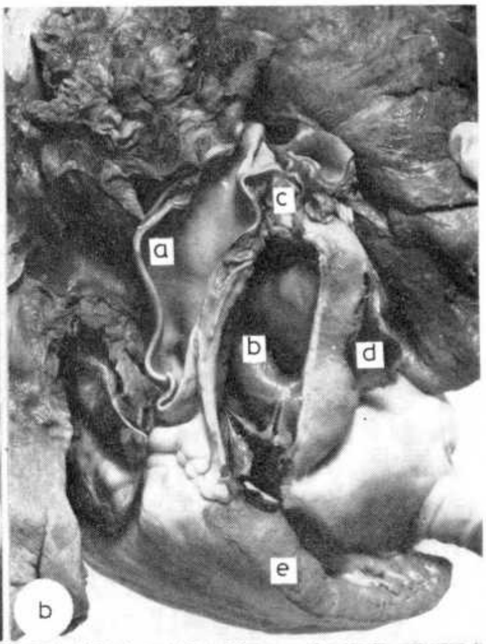
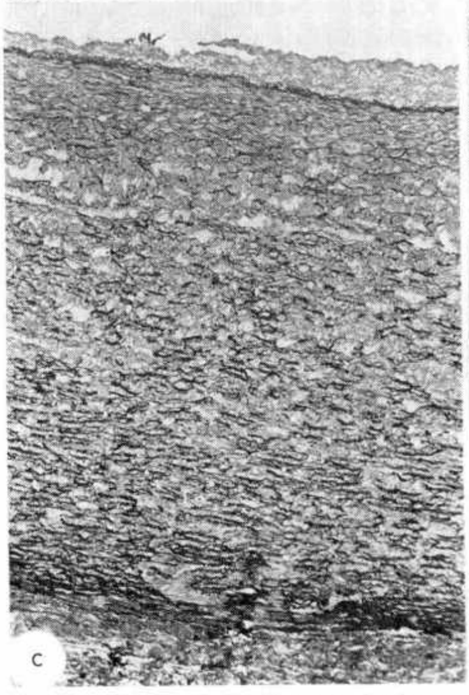


Fig. 1 *Electrocardiogram (age 11) showing right ventricular hypertrophy. Calibration 1 cm = 1 mV except V4 and V5 when 1 cm = 2 mV.*







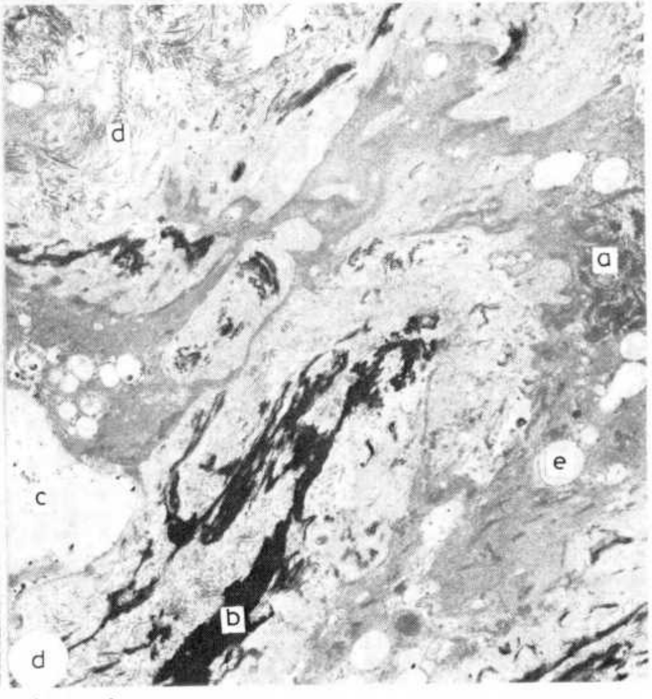


Fig. 2a *Chest* x-*ray film (age 11) showing a prominent pulmonary artery.*

Fig. 2b *The heart and major vessels at necropsy.* a, *aorta;* b, *pulmonary artery;* c, *persistent ductus arteriosus;* d, *site of rupture;* e, *right ventricle.*

Fig. 2c *Pulmonary artery adjacent to rupture showing widespread fragmentation of the medial elastic fibres. (Elastic-van Giesson ×60.)*

Fig. 2d *Pulmonary artery adjacent to rupture. (Transmission electron micrograph ×7500.)*
a, *fibroblast;* b, *elastic tissue;* c, *mucopolysaccharide;* d, *collagen;* e, *cytoplasmic vacuole.*

The elastic pulmonary arteries showed focal intimal thickening but lipid was not demonstrated and there was no evidence of atheroma, syphilis, or infection. The muscular pulmonary arteries showed changes of severe pulmonary hypertension with severe medial hypertrophy, intimal thickening, and the development of longitudinal muscle bundles internal and external to the elastic lamina. Plexiform and angiomatoid lesions were not identified but many vessels were dilated and plentiful haemosiderin-laden macrophages were present within the alveoli.

The aorta was histologically normal.

Discussion

Aneurysm of the pulmonary artery trunk or its branches is uncommon. Boyd and McGavack[1] have shown that a cardiac malformation with pulmonary hypertension is an aetiological factor in 40 per cent of such cases. Persistent ductus arteriosus is the commonest single lesion, occurring with 20 per cent of pulmonary aneurysms. The association of pulmonary hypertension with persistent ductus arteriosus is well recognised and not uncommonly mild dilatation of the pulmonary artery is observed. However, true aneurysm occurs in only 15 per cent, and a direct causative association with pulmonary hypertension is not always demonstrable. Other factors such as atheroma, endocarditis, tuberculosis, and syphilis contribute to the production of aneurysm in this condition.

In the patient described here, cystic medionecrosis was the main pathological change in the aneurysm and it is probable that this was a direct consequence of the extremely high pulmonary artery pressure.[2] The presence of fetal-type pulmonary vessels, the absence of a significant left-to-right shunt, and the small size of the ductus offer support for the theory (discussed by Whitaker *et al.*[3]) that one cause of severe pulmonary hypertension associated with persistent ductus arteriosus may be a primary persistence of fetal pulmonary vasculature, rather than simply a consequence of increased pulmonary blood flow.

A predominantly systolic murmur is not an uncommon finding in persistent ductus arteriosus when pulmonary hypertension is present,[3] and the intensity of the murmur in this patient possibly reflected the narrowness of the ductus. An unusual clinical feature was the lack of effort intolerance, and the absence of haemoptysis, despite the severity of the pulmonary hypertension.

Pulmonary artery aneurysms, especially of infective aetiology, may rupture into a bronchus or the pericardium. However, fatal rupture of an aneurysm associated with pure persistent ductus arteriosus is exceedingly rare and only six cases have been reported. Those described by Durno and Langdon Brown, and by Moench (cited in Lindert and Correll[4]) were associated with atheroma of the pulmonary artery and probable pulmonary hypertension; those reported by Hartwell and Tilden, and by d'Aunoy and van Haam (cited in Lindert and Correll[4]) were secondary to endocarditis and syphilis, respectively. Whether the cases published by Yuskis (cited in Lindert and Correll[4]) and by Lindert and Correll[4] themselves were associated with pulmonary hypertension is unknown and histological study of the aneurysm was not performed. With the exception of the syphilitic case described by d'Aunoy and van Haam the ductus was always greater than 1 cm and the appearance, position, and size of the pulmonary aneurysm were variable.

Two cases are on record of patients with persistent ductus arteriosus and pulmonary hypertension dying from a ruptured pulmonary artery aneurysm secondary to cystic medionecrosis. One had coexistent cor biatriatum triloculare and aortic hypoplasia,[5] and the other had mitral stenosis and cystic medionecrosis of the aorta.[3]

Ruptured pulmonary artery aneurysm associated with persistent ductus arteriosus and presenting as massive haemoptysis has, in one instance, been treated successfully by operation (de Camp, in Holman *et al.*[6]). It is therefore important that this complication should be considered in any patient with persistent ductus and pulmonary hypertension, especially if there are clinical features of pulmonary regurgitation.

We are grateful to Dr David Verel, consultant cardiologist, Sheffield Cardio-Thoracic Unit, Northern General Hospital, and to Dr H Pilling, HM Coroner for South Yorkshire, for kind permission to report this case. We also thank Professor M J Davies (St George's Hospital) and Dr P Carson (City General Hospital, Stoke-on-Trent) for helpful comments on this case.

References

1 Boyd LJ, McGavack TH. Aneurysm of the pulmonary artery. *Am Heart J* 1939; **18:** 562–78.

2 Spencer H. *Pathology of the lung*. 3rd ed. Oxford: Pergamon Press, 1977: 579–649.

3 Whitaker W, Heath D, Brown JW. Patent ductus arteriosus with pulmonary hypertension. *Br Heart J* 1955; **17:** 121–37.

4 Lindert MCF, Correll HK. Rupture of pulmonary

Br Heart J 1980; **44**: 469–71

Extreme right ventricular hypoplasia after relief of severe pulmonary stenosis

Use of balloon catheter occlusion of atrial septal defect in assessing right ventricular function

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SUMMARY A patient is described in whom extreme right ventricular hypoplasia and right-to-left shunting through an atrial septal defect occurred after relief of severe pulmonary stenosis. The ability of the hypoplastic right ventricle to deal with an increased volume load was assessed at cardiac catheterisation by occluding the atrial septal defect with a balloon tipped catheter.

Right-to-left interatrial shunting in the presence of normal right ventricular pressure is an unusual finding which has been described in rare congenital anomalies such as Uhl's syndrome and isolated right ventricular hypoplasia[1 2] and rarely after complete relief of pulmonary valve stenosis.[3 4] The shunting in these circumstances is attributed to an increased resistance to right ventricular filling. We describe a case with right-to-left interatrial shunting with normal right ventricular pressure and right ventricular hypoplasia after pulmonary valvotomy for pulmonary stenosis, in whom a balloon catheter was used to occlude the interatrial communication at cardiac catheterisation. This allowed assessment of the adequacy of the hypoplastic right ventricle to deal with an increased workload. Subsequent closure of a secundum atrial septal defect resulted in relief of the patient's cyanosis and effort intolerance.

Case report

A 26-year-old student presented with cyanosis and worsening effort intolerance. He had been cyanosed from birth and cardiac catheterisation at the age of 14 years had shown severe pulmonary stenosis with right-to-left shunting at atrial level. The right ventricular pressure was said to have been 280 mmHg. A pulmonary valvotomy was performed at that time giving some relief of symptoms for about a year, after which they recurred. On examination he was a well-developed man with grade IV cyanosis and clubbing of the fingers and toes. The pulse was 96 a minute, regular, and of normal volume and character. The venous pulsation showed a prominent "a" wave, blood pressure 140/80 mmHg. There was no parasternal heave, the apex was impalpable. The first heart sound was normal, the second widely and fixedly split. There was a grade 1/6 soft mid-systolic murmur at the upper left sternal edge. There were no other abnormal physical signs. The haemoglobin was 22 g. Electrocardiograms showed sinus rhythm, with evidence of right atrial hypertrophy and high left ventricular voltage (R=31 mm in V5, S=23 mm in V1) with ST and T wave changes in leads V3 to V6. A chest *x*-ray film showed moderate cardiac enlargement with normal lung fields. At cardiac catheterisation a 14 mmHg right atrial "a" wave and a right ventricular pressure of 24/9 to 12 mmHg were shown with no significant gradient across the pulmonary valve. There was right-to-left shunting at atrial level, resulting in a systemic arterial saturation of 82 per cent, the ratio of systemic to pulmonary blood flows being 1·7:1. The interatrial defect was occluded by inflating a no. 7 balloon catheter in the left atrium and pulling it against the septum. This manoeuvre eliminated shunting and allowed the arterial oxygen saturation to reach 97 per cent with obvious relief of the cyanosis. This occlusion was maintained for 20 minutes with no adverse haemodynamic changes or conduction disturbances. A right ventricular angiogram indicated a small, thick-walled, poorly contracting right ventricle.

At operation (Mr C Lincoln) on cardiopulmonary bypass, a secundum atrial septal defect measuring

1×1 cm was closed by direct suture through a right atrial approach. The postoperative course was uneventful and the patient's symptoms were relieved. Repeat cardiac catheterisation showed normal haemodynamics at rest and on exercise, apart from a 15 mmHg right atrial "a" wave and a 10 mmHg gradient across the pulmonary valve; there was no evidence of intracardiac shunting. An electrocardiogram a month after the operation showed a decrease in P wave amplitude in lead II from 4 to 2 mm, with ST-T wave changes attributable to the pericardiotomy. He has remained well at follow-up to date, with a haemoglobin of 13 g, apart from one episode of supraventricular tachycardia which responded rapidly to carotid sinus massage.

Discussion

Pulmonary valvotomy is usually performed early in severe pulmonary stenosis, particularly if complications such as right ventricular failure have occurred. If it is performed before overt right ventricular failure, postoperatively right ventricular function may be normal,[5] while if operation is delayed myocardial fibrosis and right ventricular systolic or diastolic dysfunction is likely. This continued right ventricular dysfunction postoperatively is probably multifactorial. Preoperative factors causing right ventricular dysfunction include poor coronary blood flow caused by extreme ventricular hypertrophy relative to the amount of coronary capillary circulation, the fixed size of the coronary ostia, the extremely high pressures in the right ventricular wall preventing any coronary blood flow during systole, and the decreased pressure gradient across the coronary bed produced by an increase in the right atrial pressure and right ventricular diastolic pressure[6]; operative factors particularly the efficacy of myocardial protection and in addition whether or not a ventriculotomy is performed are also important.[7 8] If diastolic dysfunction is predominant, there may be continued "indistensibility" of the right ventricle because of poor compliance leading to a high right ventricular filling pressure.[3 4] In the presence of an interatrial communication, either a patent foramen ovale or an atrial septal defect, the high right ventricular filling pressure, if it exceeds the left ventricular filling pressure, will cause right-to-left shunting at atrial level, regardless of the relative ventricular systolic pressures, with consequent arterial desaturation and, maybe, clinical cyanosis.

Right-to-left shunting at atrial level is not rare in severe pulmonary stenosis,[9–11] and is a cause of cyanosis in this condition. It is almost invariably relieved after pulmonary valvotomy when the right ventricular filling pressure falls.[11] Continued right-to-left shunting after pulmonary valve surgery is, however, rare.[3 4] Its incidence varies but Oakley *et al.*[3] described it in six cases out of their series of 56 pulmonary valvotomies. When it occurs reoperation is recommended to close the interatrial shunt, whether a valve patent foramen ovale or an atrial septal defect, to avoid the possibility of paradoxical emboli and to avoid the sequelae of polycythaemia. The results of closing such a defect however, are not always predictable, as the right ventricle may not be able to cope with the increased workload, particularly if there is a degree of right ventricular hypoplasia, and right ventricular failure may result.[12]

Although right ventricular dysfunction is well recognised after relief of long-standing pulmonary stenosis, frank right ventricular hypoplasia which can also occur is very unusual and less well described.[12–14] When it is present it may be helped by the volume loading which occurs if pulmonary regurgitation is caused at pulmonary valvotomy.[13]

The use of balloon tipped catheters to close interatrial communications has been advocated in patients with isolated right ventricular hypoplasia in order to assess the possible effects on the right ventricle of surgical closure of the defects.[1 2] As far as we know, this is the first case of interatrial shunting after pulmonary valvotomy where this manoeuvre has been used to advantage in showing that, though the right ventricle was relatively hypoplastic, it could, nevertheless, cope with the increased workload.

We are grateful to Mr Christopher Lincoln for permission to report this case.

References

[1] Van der Hauwaert LG, Michaelsson M. Isolated right ventricular hypolasia. *Circulation* 1971; **44:** 466–74.

[2] Haworth SG, Shinebourne EA, Miller GAH. Right-to-left interatrial shunting with normal right ventricular pressure—a puzzling haemodynamic picture associated with some rare congenital malformations of the right ventricle and tricuspid valve. *Br Heart J* 1975; **37:** 386–91.

[3] Oakley CM, Braimbridge MV, Bentall HH, Cleland WP. Reversed interatrial shunt following complete relief of pulmonary valve stenosis. *Br Heart J* 1964; **26:** 662–70.

[4] de Castro CM, Nelson WP, Jones RC, Hall RJ, Hopeman AR, Jahnke EJ. Pulmonary stenosis, cyanosis, interatrial communication and inadequate right ventricular distensibility following pulmonary valvotomy. *Am J Cardiol* 1970; **26:** 540–3.

[5] Stone FM, Bessinger FB Jr, Lucas RV Jr, Moller JH. Pre- and postoperative rest and exercise hemodynamics

in children with pulmonary stenosis. *Circulation* 1974; **49:** 1102–6.
[6]Schlant RC. In Hurst JW, ed. *The heart.* New York: McGraw-Hill, 1978: 822.
[7]Johnson AM. Impaired exercise response and other residua of pulmonary stenosis after valvotomy. *Br Heart J* 1962; **24:** 375–88.
[8]Finnegan P, Ihenacho HNC, Singh SP, Abrams LD. Haemodynamic studies at rest and during exercise in pulmonary stenosis after surgery. *Br Heart J* 1974; **36:** 913–8.
[9]Abrahams DG, Wood P. Pulmonary stenosis with normal aortic root. *Br Heart J* 1951; **13:** 519–48.
[10]Callahan JA, Brandenberg RO, Swan HJC. Pulmonary stenosis and interatrial communication with cyanosis; hemodynamic and clinical study of 10 patients. *Am J Med* 1955; **19:** 189–202.
[11]Brock R. The surgical treatment of pulmonary stenosis. *Br Heart J* 1961; **23:** 337–56.
[12]Williams CB, Barrett-Boyes BG, Lowe JB. Underdeveloped right ventricle and pulmonary stenosis. *Am J Cardiol* 1963; **11:** 458–68.
[13]Rao PS, Liebman J, Borkat G. Right ventricular growth in a case of pulmonary stenosis with intact ventricular septum and hypoplastic right ventricle. *Circulation* 1976; **53:** 389–94.
[14]Rowe RD. Pulmonary stenosis with normal aortic root. In: Keith JD, Rowe RD, Vlad P, eds. *Heart disease in infancy and childhood* 3rd ed. New York: Macmillan, 1978: 762.

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International Symposium on Nuclear Cardiology

This will take place on 6 to 10 September 1981 in Tel Aviv, Israel.

For further information write to: The Secretariat, POB 29784, Tel Aviv, Israel.

International symposium of ultrasound in cardiology

This symposium will take place on 27 to 28 February 1981 in Madrid, Spain, at the Centro Especial Ramon y Cajal. It is organised by the echocardiography section of the Spanish Society of Cardiology.

Deadline for submitting abstracts, 30 November 1980.

Further information can be obtained from: International Symposium of Ultrasound in Cardiology, Secretariat: Central de Congresos, SA, Av General Peron 26, Madrid-20, Spain.

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Details from: The Postgraduate Secretary, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE.

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This symposium will be held in Utrecht, the Netherlands, from 25 to 27 May 1981. The symposium is sponsored by the Netherlands Heart Foundation.

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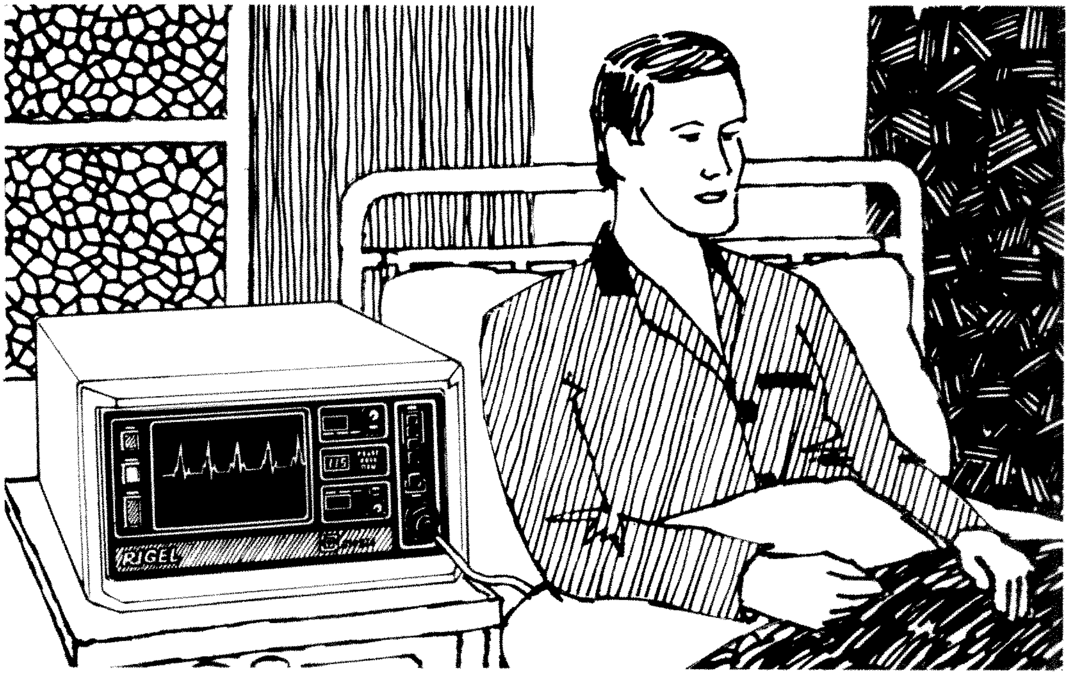

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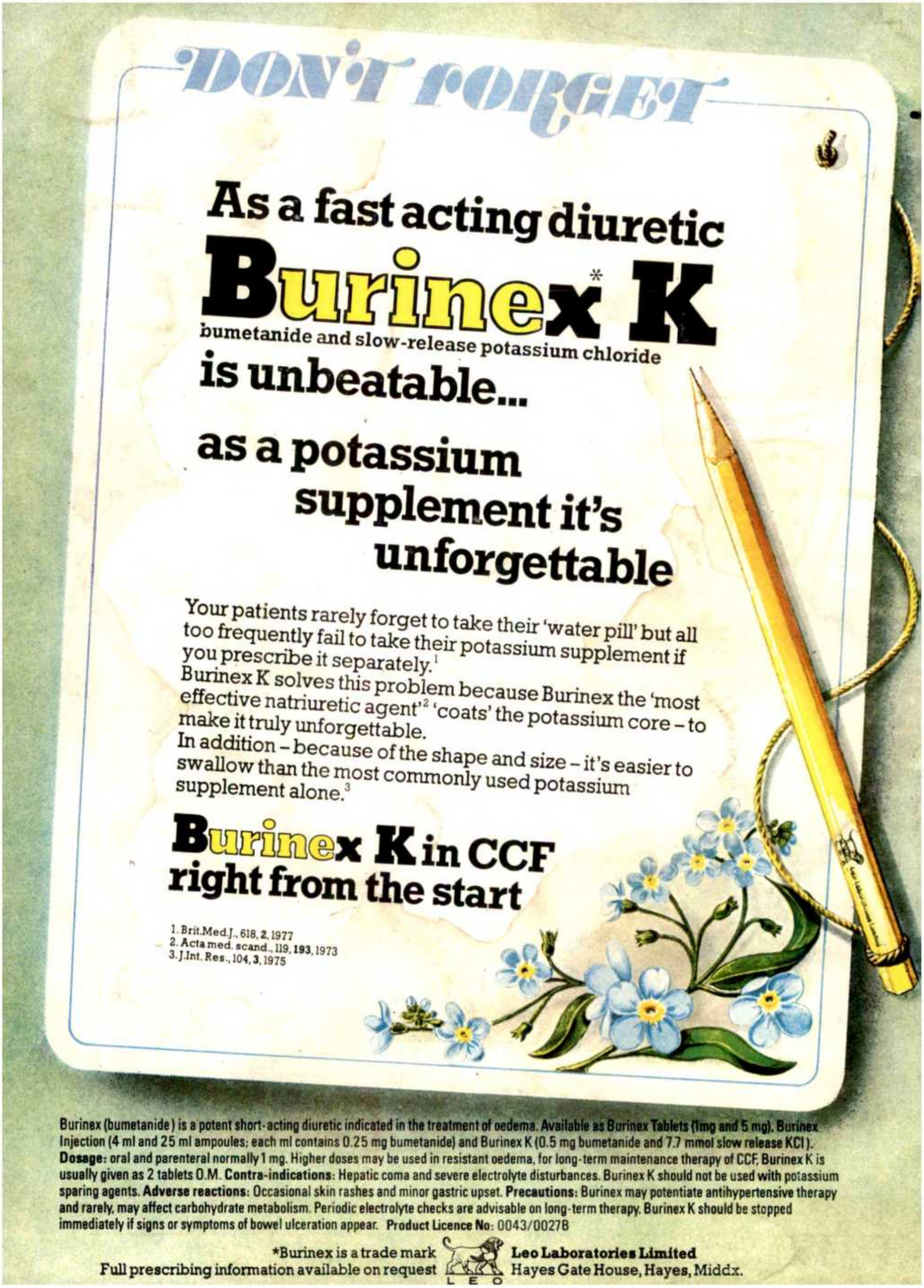

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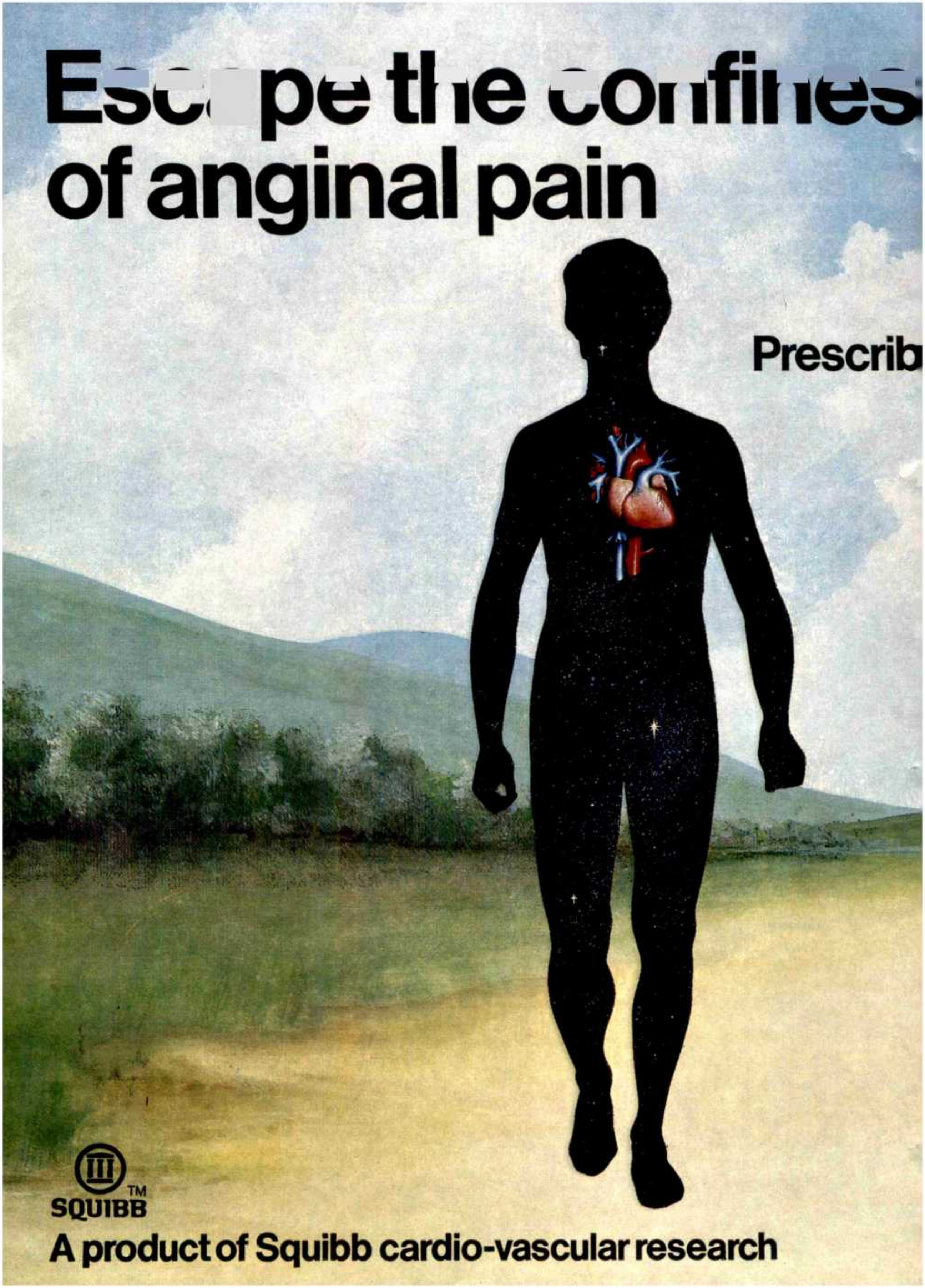
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Side-effects:
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Overdosage:
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40 mg – PL0037/0098
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References:
1. Livesley B., et al., BMJ, 1973, I: 375-378.
2. Bala Subramanian V., et al., Lancet 1980, I: 841-844.
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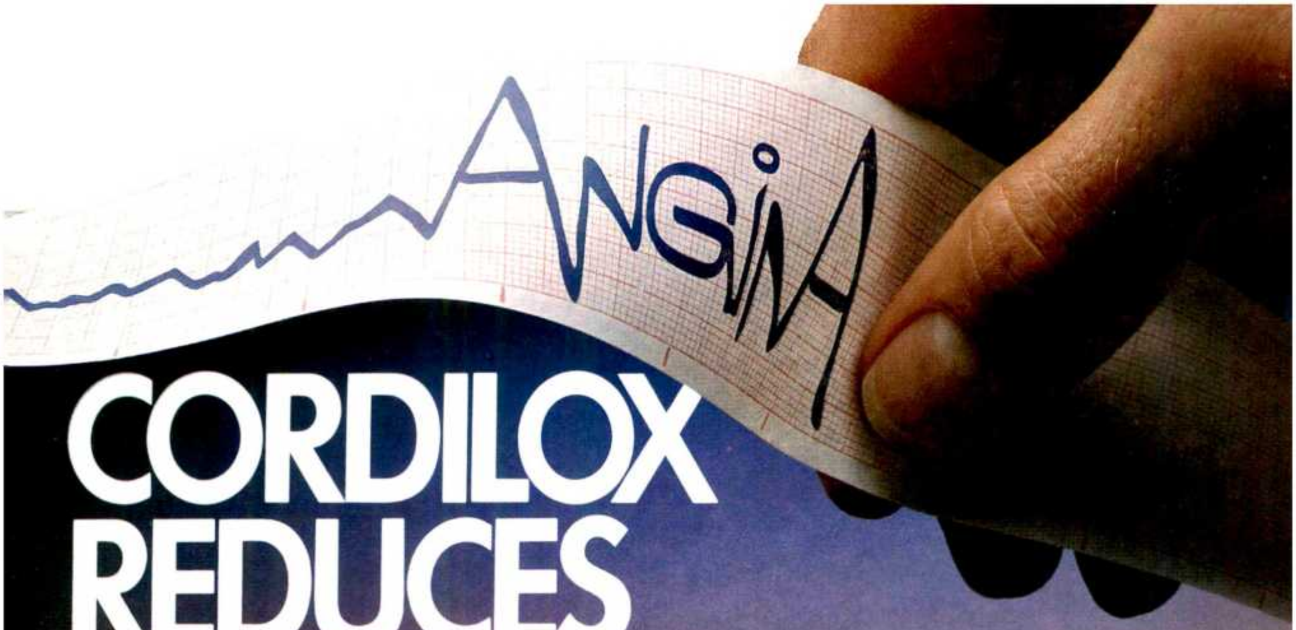

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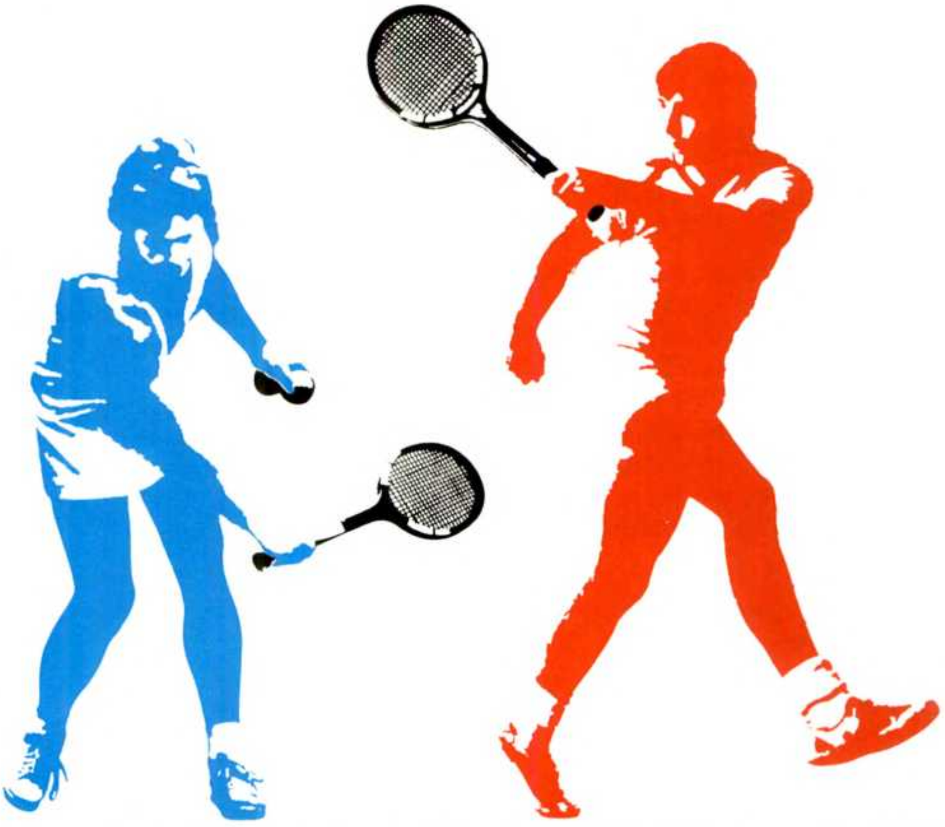

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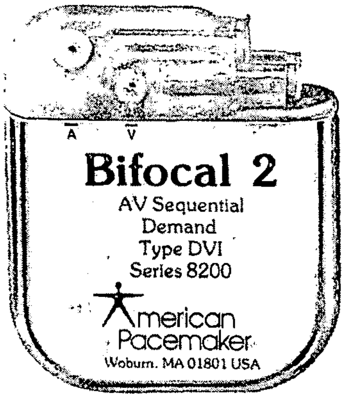

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Br Heart J 1980; **44:** 473–87

Adaptation of hypertensives to treatment with cardioselective and non-selective beta-blockers

Absence of correlation between bradycardia and blood pressure control, and reduction in slope of the QT/RR relation

E M VAUGHAN WILLIAMS, M O HASSAN, J S FLORAS,* P SLEIGHT, J V JONES

From the University Department of Pharmacology, and the Department of Cardiovascular Medicine, John Radcliffe Hospital, Headington, Oxford

SUMMARY Thirty mild hypertensives were treated for more than two months with either cardioselective (atenolol or metoprolol) or non-selective (propranolol or pindolol) beta-blockers; the patients were assigned to the drugs in a double-blind manner. A procedure was designed to distinguish between the effects of the drugs themselves while treatment continued, and the development of adaptive changes which would persist when the drugs had been eliminated from the body. Though individual responses to treatment varied in both groups, the mean effect of the cardioselective and non-selective drugs in the control of hypertension was similar. There was no evidence of the development of supersensitivity or "rebound". On the contrary, an adaptive bradycardia (that is a fall of not less than 10% in heart rate persisting 52 hours after stopping treatment) was observed at rest in 17/30 patients, and peak heart rates and blood pressures during exercise were lower in both groups than before treatment. Cardioselective drugs induced a significantly greater bradycardia at rest than non-selective, but on exercise increases in heart rate were reduced more by the non-selective drugs, so that the same peak heart rates were reached on exercise in both groups. Adaptation also affected QT. The results suggest that two factors govern the shortening of QT by increases in heart rate, a "metabolic" effect, determined by sympathetic drive, and a "biophysical" effect determined by heart rate. The adrenergic effect is attenuated by acute beta-blockade, or by adaptation to prolonged blockade, leaving a shallow, rate-determined, slope to the QT/RR regression.

The efficacy of beta-receptor blocking drugs in the treatment of hypertension was discovered more than 15 years ago.[1 2] After an initial period of doubt,[3] beta-blockade became accepted as a major therapeutic procedure,[4 5] yet there is no universal agreement concerning its mechanism of action. There is abundant evidence, however, that the effect is a consequence (though often delayed) of the blockade of beta_1-receptors since cardioselective compounds[6 7] reduce blood pressure. Though cardiac output usually falls initially, and peripheral resistance increases, it has been found that after prolonged treatment the cardiac output may return to normal levels in spite of a persistent lowering of blood pressure, indicating a reduction of peripheral resistance.[8–11] Thus beta-adrenoceptor blockade must be responsible for some hypotensive action apart from a reduction of cardiac output, even though, in some other studies, it was found that cardiac output did remain moderately subnormal.[7 12]

It was suggested that the fact that beta-blockers reduce or prevent adrenergically-stimulated release of renin might be responsible for their hypotensive action,[13] yet later studies failed to show any consistent relation between levels of plasma renin

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* Rhodes Scholar.

Received for publication 28 April 1980

activity and the efficacy of beta-blockers in hypertension.[14–18]

Another hypothesis advanced to explain the effect of beta-blockers in hypertension was that they may have a direct acute action on the central nervous system[19] causing a reduction in the outflow of sympathetic impulses by blocking beta-receptors in the brain. The effect was not observed with practolol, however, which does not substantially cross the blood-brain barrier, yet practolol is effective in hypertension.

The pharmacological analysis of the mode of action of drugs in animals is usually based upon the results of acute experiments. In man, beta-blockers are administered for weeks, months, or years. Moreover, the optimal beneficial effect of beta-blockers in hypertension is not usually immediately apparent. Prichard and Gillam[20] stated: "In the moderate and severe hypertensive treated with oral propranolol, though there is immediate full cardiac slowing, the full hypotensive effect is often delayed up to one or two months". Furthermore, in many patients bradycardia persists for some days after treatment has been stopped, and the hypotensive effect may persist even longer. Zacharias and Cowen,[4] in their study of propranolol in hypertension, expressed the opinion: "That a second factor is involved is suggested by the fact that even when patients have been off propranolol for 16 weeks their mean blood pressure did not rise to untreated levels".

It seemed logical, therefore, to study the effects of beta-blockers in animals which had been treated for prolonged periods. In order to distinguish a secondary adaptation to the drug from its acute effects, treated animals were killed at least 24 hours after the last dose, when the drug would have been eliminated from the body, and their hearts were then removed for electrophysiological and other investigations. The results of several such studies, initiated in 1972, indicated that prolonged beta-blockade produced several adaptive changes,[21] the most prominent of which were a large prolongation of action potential duration,[22] and an increase in the vascularity of the myocardium.[23] The experiments were carried out in rabbits, and it was naturally of interest to discover what, if any, adaptive responses occurred after prolonged beta-blockade in man. Though there have been numerous studies of the effects of long-term blockade, these have usually been carried out while the treatment continued.[8 9 12 24] In order to distinguish adaptive changes from the direct effects of the drugs, however, it is necessary to interrupt the treatment for a sufficient time to permit elimination of the compounds from the body before measurements are made.

This paper reports the effects of treatment with four beta-blockers (two cardioselective, two non-selective) in 30 mildly hypertensive patients. The main findings were that adaptive changes did occur, and that a clear distinction could be made between the effects of the cardioselective and non-selective agents. There was no correlation between the persistent bradycardia, when it occurred, and the hypotensive response. Furthermore, after acute intravenous blockade at any time, or after adaptation to blockade but in the absence of the drug, the slope of the regression relating the QT to the RR interval was reduced, especially during exercise.

Methods

SELECTION OF PATIENTS

Forty-seven untreated patients, referred for assessment of possible hypertension, agreed to participate in the study. Cuff blood pressure readings of 140/90 mmHg or more had been recorded on at least three occasions, either by their general practitioners or in the hospital outpatient clinic. Intra-arterial pressure was recorded for 24 hours,[25] and after computer analysis 17 of the patients were found to have pressures of less than 140/90 mmHg for 70 per cent or more of the working day, and were classified as normotensives. The remaining 30 patients (19 male, 11 female) were also included in a larger trial of the relative efficacy of various beta-blockers in hypertension, and were assigned in a double-blind manner to receive orally one of four beta-blockers, long-acting propranolol,[7] pindolol,[7] atenolol,[7] and metoprolol.[9] They were instructed to take their medication each morning, but to refrain from doing so on days 7 and 8, and on days 28 and 29 of the trial. The initial dosage was 160 mg of long-acting propranolol, 15 mg pindolol, 100 mg atenolol, or 200 mg metoprolol. On the 16th day blood pressure was measured in the clinic, and dosage was adjusted (decreased in two, increased in 14). Blood pressure was again measured in the clinic on the 42nd and 70th days.

The mean age of the patients was 44·8 years (range 16 to 69, SD 13·4). The nature of the trial was ex-explained to them and written consent to their participation obtained. Their responses to exercise before and after administration of an intravenous injection of their assigned beta-blocker were measured on days 1, 8, and 29, in accordance with the following procedure.

PROCEDURE

Systolic and diastolic blood pressures were measured with a sphygmomanometer, and an electrocardiogram was recorded (lead II, Hewlett-Packard

1511A, 50 mm/s) while the patient rested in a seated position. The electrocardiogram was monitored continuously and records were obtained after three minutes of treadmill (Avionics E15) exercise at 2·9 kph and 10 per cent incline (exercise 1), and after three minutes at 4·0 kph at 12 per cent incline (exercise 2). Systolic and diastolic blood pressure were again measured after the peak of exercise 2 (at a standard time, 40 to 50 s after exercise).

The patients then rested for a few minutes seated, and were given, by intravenous injection, either propranolol 1 mg (in 1 ml over 2 min), pindolol 0·4 mg (in 2 ml over 2 min), atenolol 5 mg (in 10 ml over 5 min), metoprolol 10 mg (in 10 ml over 5 min), the drug selected being the same as that with which they were being treated.

After a further 10 to 15 minutes the electrocardiogram and blood pressure were recorded at rest, and after two periods of exercise as described above.

The patients were submitted to this procedure on day 1, before the start of treatment; on day 8, 52 hours after their most recent oral dose (taken on day 6); and on day 29, again 52 hours after their most recent dose, taken on day 27. All patients completed the procedure. One patient complained of breathlessness during the 6th minute on one occasion; another complained of leg pain on one occasion.

TREATMENT OF DATA

Before the code was broken, measurements of three QT and RR intervals at each of the six stages of the procedure (rest; exercise 1; exercise 2; and after the intravenous beta-blocker, rest; exercise 1 and exercise 2) were made by two observers independently, and averaged. The QT interval was defined as the distance between the beginning of the Q wave and the point at which a tangent to the descending limb of the T wave crossed the baseline. The RR interval was measured from the peaks of the R waves. There was no interobserver variation. All measurements of blood pressure were made, and all injections administered, by one of us (MOH).

Sixty-six observations were obtained from each patient. In view of the small number of patients on each drug, interest was concentrated upon detecting any differences in responses to the selective (atenolol, metoprolol) and non-selective (propranolol, pindolol) beta-blockers, and particular attention was paid to comparisons between the groups receiving these drugs. All the raw data were entered on tape, and analysed by various specially-made programs with an HP 9830 computer. Responses to individual drugs, and to all drugs, were calculated and compared. Linear and polynomial regressions were computed. The main points of interest have been extracted and are presented here. The significance of differences between groups was calculated by Student's t test, and of differences within patients by a paired t test.

Results

(1) CONTROL OF BLOOD PRESSURE AT REST

The systolic and diastolic pressures measured initially, and on the 16th, 42nd, and 70th days of the trial, are presented in Table 1. These measurements were made while the patients were still taking the drug, a few hours after their daily dose. By good fortune the groups selected at random for treatment with the non-selective and cardioselective drugs were extremely well matched, with identical initial mean systolic and diastolic blood pressures. Control of blood pressure was satisfactory in both groups, the onset of control appearing a little earlier in the patients in the cardioselective group. The hypo-

Table 1 *Control of blood pressure*

Day 1 *Mean ±SE*	*Day 16* *Percentage change ±SE*	*p value*	*Day 42* *Percentage change ±SE*	*p value*	*Day 70* *Percentage change ±SE*	*p value*
(A) Patients treated with propranolol or pindolol (non-selective) 9M, 5F						
Systolic blood pressure						
173·0 ±8·65	−8·3 ±7·2	0·27	−7·9 ±3·3	0·036	−13·2 ±4·0	0·007
Diastolic blood pressure						
109·7 ±3·63	−4·9 ±2·4	0·058	−10·6 ±2·6	0·0017	−16·2 ±2·7	0·00006
(B) Patients treated with atenolol or metoprolol (cardioselective) 10 M, 6 F						
Systolic blood pressure						
172·0 ±6·5	−9·9 ±3·2	0·008	−14·4 ±2·4	0·00004	−18·4 ±3·0	0·00003
Diastolic blood pressure						
109·8 ±3·6	−13·9 ±3·3	0·0009	−16·4 ±3·3	0·0002	−21·0 ±2·4	10^{-5}

NB—Statistical significances were calculated by a paired t test. Measurements in column 1 have been given in mmHg (1 mmHg = 0·133 kPa).

tensive effect appeared to be slightly larger with the cardioselective drugs, but the differences in reduction of mean systolic (–13·2 versus –18·4%) and of mean diastolic pressure (–16·2 versus –21·0%) were not, in fact, statistically significant (p=0·31 and 0·2, respectively). Thus, so far as the mean control of blood pressure was concerned there was little to choose between selective and non-selective drugs. There were, however, as might be expected from previous reports, some patients in each group whose response to treatment was minor. If an arbitrary criterion of a fall of less than 10 mmHg systolic and 5 mmHg diastolic is taken as constituting a minor response, then the incidence of minor responses was, for systolic pressures, for propranolol 2/7, and for pindolol 3/7; for atenolol 1/7, and for metoprolol 1/9. Only one patient (on metoprolol) had a fall of diastolic pressure of less than 5 mmHg.

(2) ADAPTATION OF BLOOD PRESSURE DURING TREATMENT, AT REST, AND ON EXERCISE

Measurements were made initially before the start of treatment (day 1) and, 52 hours after the most recent medication, on days 8 and 29. The results are presented in Table 2, and indicate a small difference in the effects of the non-selective and cardioselective drugs. The first two columns indicate that, with both groups of drugs, neither systolic nor diastolic pressures at rest returned to initial levels 52 hours after the last dose of drug, even after only one week's treatment, though the only statistically significant fall was of the systolic pressure in the cardioselective group. During exercise, however, there was a clear distinction between the groups. The *rise* in systolic pressure during exercise was significantly less pronounced on day 8 and day 29 in the non-selective group, but was not significantly altered in the cardioselective group. (As already mentioned the *absolute* levels reached during exercise were lower in both groups than before treatment.) There was hardly any change in diastolic pressure in either group during exercise on day 1 but on day 29 in the non-selective group diastolic pressure fell, but was still unchanged in the cardioselective group.

Table 2 *Adaptation of blood pressure at rest and during exercise (52 hours after last dose)*

	Percentage change in resting blood pressure		*Percentage change in blood pressure (from rest) during second exercise*		
	Day 8	*Day 29*	*Day 1*	*Day 8*	*Day 29*
(A) Non-selective beta-blockers					
Systolic					
Mean	−7·8	−8·9	+15·9	+6·2	+4·4
SE	6·2	6·2	3·2	2·6	2·1
			Difference from day 1	−9·7	−11·5
p value	0·2	0·17		0·012	0·0005
Diastolic					
Mean	−2·4	−5·0	+2·2.	−0·7	−5·8
SE	3·6	3·03	1·3	1·4	2·1
			Difference from day 1	−2·9	−8·0
p value	0·47	0·86		0·19	0·009
(B) Cardioselective drugs					
Systolic					
Mean	−9·3	−10·1	+9·8	+5·6	+6·1
SE	5·6	7·5	2·5	2·2	2·6
			Difference from day 1	−4·2	−3·7
p value	0·019	0·016		0·18	0·22
Diastolic					
Mean	−5·4	−5·1	−0·9	−2·7	−1·3
SE	2·3	4·3	2·3	1·5	2·0
			Difference from day 1	−1·8	−0·4
p value	0·09	0·15		0·5	0·9

(3) ADAPTIVE CHANGES IN HEART RATE

There was a striking and highly significant difference in the adaptation of heart rate to treatment with non-selective and cardioselective drugs, presented in Table 3. With the non-selective drugs, 52 hours after the last dose, there was only a small number of patients with persistent bradycardia at rest, not statistically significant for the group as a whole. During exercise, however, in spite of the fact that no drug could have remained in the body (since both propranolol and pindolol have short metabolic half lives) there was a remarkable reduction of the heart rate increases in response to exercise, at both levels of effort.

In contrast, in the cardioselective group, there was a pronounced and statistically significant bradycardia at rest. On exercise, however, the *increases* in heart rate when expressed as a percentage increase from the resting heart rate were just as large as they were initially, a fact that confirms, incidentally, that no drug could still be present after 52 hours, even though the half life of atenolol is longer than that of the other drugs.[26] (The mean increases in heart rate during the second exercise in the seven patients on atenolol were +44·6% on day 8 and +47·3% on day 29, as compared with +49% on day 1).

Thus the interesting result was obtained that the actual heart rates during exercise in the two groups were not significantly different from each other after treatment, though in both groups the peak rates reached were lower than those observed before treatment was started. In the cardioselective group, the heart rates were lower at rest, but increased on exercise (to a mean during exercise 2, day 29, of 107·9 ±5·6 beats/min, in comparison with 129·3 before treatment) whereas in the non-selective group the resting heart rates were not significantly lowered, but rose less on exercise (to a mean during exercise 2, day 29, of 105·6 ±4·1, in comparison with 123·2 before treatment).

(4) ADAPTATION OF BLOOD PRESSURE AND HEART RATE TO ACUTE INTRAVENOUS BLOCKADE

Blood pressure

The immediate response to acute beta-blockade has often been reported to be a fall in cardiac output with increased peripheral resistance, resulting in no change in blood pressure. Column 1 of Table 4A and B, confirms the absence of significant blood pressure change, and indicates that there is no difference between the non-selective and cardioselective compounds in this respect. Table 4 also indicates that there is virtually no change in sensitivity to the effects of acute blockade on blood pressure, either at rest or during exercise. The only significant blood pressure statistic in the whole table is a slightly larger fall in systolic pressure at rest in response to intravenous beta-blockade in the non-selective group. The table indicates no developing supersensitivity (or decreased sensitivity) to acute blockade, in respect of systolic and diastolic blood pressure.

Heart rate

An acute injection of propranolol on day 1 did not reduce heart rate at rest, but lowered the increase in heart rate in response to exercise 2 from +45·3 to +33·3 per cent. There was no significance adaptive change during treatment in sensitivity to acute intravenous administration of propranolol at rest or during exercise, which is in contrast to the finding of Brundin *et al.*[27] A similar result was obtained for the non-selective group as a whole.

Acute injection of the cardioselective drugs, however, did cause an immediate bradycardia at rest, and this result was significantly different from that of the non-selective compounds. This bradycardic response was not significantly less on day 29. On exercise 2 acute blockade reduced the increase in heart rate from +46·1 to +34·8 per cent on day 1, and from +49·3 to +38·4 per cent on day 29, again showing an absence of adaptation.

Thus, even if prolonged beta-blockade increases the number of beta-receptors, such an increase does not appear to produce, at least at the doses employed in this study, any functional adaptation to the effects of an acute injection of beta-blocker, selective or non-selective, either on heart rate or blood pressure.

(5) EFFECTS ON QT INTERVAL

(A) *Initial QT/RR relation*

Prolonged treatment of rabbits with beta-blockers at clinical dose levels causes a lengthening of action potential duration, independently of heart rate, in both young[22] and adult animals.[28] It seemed possible, if a similar adaptive response were to occur in man, that it might be detected as a prolongation of QT interval. Raine and Pickering[24] reported that QT at rest was significantly longer in patients on long-term beta-blockade (with various drugs) than in matched controls, and that QT shortened less in these patients during exercise than in controls. There was, however, no record of the pretreatment QT intervals of the patients treated with beta-blockers, and since measurements were recorded while the subjects were still on medication there was no way of distinguishing the effects of the beta-

Table 3 *Adaptation of heart rate at rest and during exercise (measured 52 hours after last dose)*

	Percentage change in resting heart rate		*Percentage change in heart rate during first exercise*			*Percentage change in heart rate during second exercise*		
	Day 8	*Day 29*	*Day 1*	*Day 8*	*Day 29*	*Day 1*	*Day 8*	*Day 29*
(A) Non-selective drugs								
Mean	−4·1	−3·3	+33·8	+23·5	+21·1	+43·7	+35·4	+28·2
SE	3·4	4·1	4·3	3·9	2·8	4·9	5·3	4·2
			Difference from day 1	−10·2	−12·1	Difference from day 1	− 8·3	−15·4
p value	0·29	0·29		0·009	0·004		0·097	0·0005
(B) Cardioselective drugs								
Mean	−9·9	−16·3	+28·4	+28·6	+30·1	+46·1	+44·6	+49·3
SE	4·2	3·3	3·6	4·9	5·3	4·5	6·4	6·9
			Difference from day 1	+ 0·2	+ 1·7	Difference from day 1	− 1·6	+ 3·2
p value	0·007	0·00004		0·97	0·77		0·77	0·61

Table 4 *Adaptation of blood pressure and heart rate to acute beta-blockade (iv)*

	Percentage change in pressure at rest			*Percentage change in pressure during exercise*		
	Day 1	*Day 8*	*Day 29*	*Day 1*	*Day 8*	*Day 29*
(A) Non-selective group						
Systolic						
Mean	−3·1	−5·1	− ·7	+10·1	+9·4	+12·2
SE	1·5	1·5	1·3	2·2	2·4	2·3
Difference from day 1		−2·0	−5·5		−0·7	+ 2·1
p value		0·23	0·03		0·85	0·41
Diastolic						
Mean	+2·6	+0·8	−3·6	+ 1·0	−2·0	− 0·1
SE	2·5	1·4	2·4	1·9	1·4	2·0
Difference from day 1		−1·7	−6·2		−3·0	− 1·1
p value		0·53	0·15		0·12	0·6
(B) Cardioselective group						
Systolic						
Mean	−3·8	−5·0	−4·3	+ 8·2	+4·5	+ 4·8
SE	2·2	2·0	2·4	2·4	2·2	2·5
Difference from day 1		−1·2	−0·5		−3·7	− 3·3
p value		0·5	0·78		0·11	0·24
Diastolic						
Mean	+1·8	−0·3	0·00	− 1·3	−3·3	− 2·1
SE	2·7	1·9		2·0	2·0	2·8
Difference from day 1		−2·2			−1·9	− 0·8
p value		0·49			0·38	0·8

(C) Heart rate
Adaptation to acute intravenous beta-blockade (52 hours after last dose)

	Percentage change in heart rate at rest			*Percentage change in heart rate on exercise*		
	Day 1	*Day 29*	*p value*	*Day 1*	*Day 29*	*p value*
Propranolol alone	0·0 ±3·3	−7·8 ±4·2	0·18	+33·3 ±4·1	+35·8 ±6·0	0·63
Propranolol+pindolol	−4·0 ±2·5	−4·6 ±2·5	0·88	+32·4 ±2·5	+29·1 ±3·7	0·41
Atenolol+metoprolol	−13·0 ±1·3	−10·0 ±3·0	0·32	+34·8 ±4·3	+38·4 ±5·1	0·44
Difference between non-selective and cardioselective	9·0	5·4		2·4	9·3	
p value	0·002	0·19		0·64	0·16	

blockers themselves from an adaptation to the blockade.

The QT interval is traditionally corrected according to the equation derived from the work of Bazett,[29] $QT_C = QT/\sqrt{RR}$, QT and RR being expressed in seconds. The initial QT_c intervals in our patients, calculated according to this equation, varied from 0·373 to 0·482 which suggests that this correction procedure may not be appropriate for hypertensive patients. Correlations were, therefore, calculated between QT and RR, QT and $\sqrt{RR}$, for both linear and polynomial regressions. Similar calculations were made on all measurements of QT and RR obtained during the trial, and, since the linear relation was simplest and fitted the points equally well, the other calculated regressions have not been presented here.

The initial values of QT and RR (in ms) at rest have been plotted for all patients in Fig. 1, appropriate symbols indicating the drug to which each patient was subsequently assigned (P, propranolol; V, pindolol; A, atenolol and M, metoprolol). The plus signs depict the least-squares fit for a linear regression, and the asterisks plot a second order polynomial. Both lines were calculated from all the results, and had correlation coefficients of 0·769 and 0·77, respectively. (A plot of QT against $\sqrt{RR}$ also had a correlation coefficient of 0·77.) The regression equations for QT/RR before treatment (day 1) for all patients at rest, and for patients assigned to non-selective and cardioselective drugs at rest and at the peak of the second exercise, are set out in Table 5.

It is apparent that the QT/RR regressions were similar for both groups, and that on exercise the

Table 5 *Initial QT/RR regressions*

Rest		
All patients	(QT)=(RR)×0·192+227	(r=0·769)
Non-selective	(QT)=(RR)×0·202+214	(r=0·821)
Cardioselective	0·195+230	0·753
Exercise		
Non-selective	(QT)=(RR)×0·242+175	(r=0·866)
Cardioselective	0·354+130	0·881

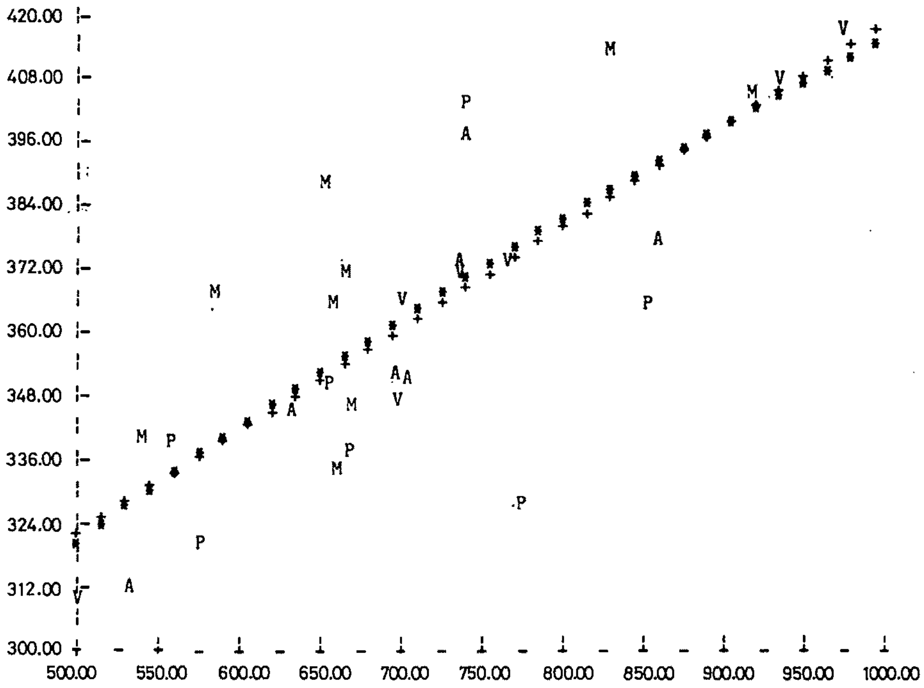

Fig. 1 *QT interval plotted against RR, all patients, at rest, before treatment, Ordinate: QT, ms. Abscissa: RR, ms. Symbols indicate drugs to which patients were subsequently assigned. P, propranolol; V, pindolol; A, atenolol; M, metoprolol. Plus signs: plot of calculated linear regression. Asterisks: plot of second order polynomial.*

regressions were steeper and the correlation coefficients higher. Also of interest, in view of what is reported below, is the fact that on exercise on day 1 the QT/RR slope appeared steeper in the group subsequently assigned to cardioselective drugs.

(B) *Adaptation to treatment*

These was a difference between the responses of the non-selective and cardioselective groups in the QT/RR relation.

In Fig. 2 the calculated linear regressions for QT/RR at rest have been plotted for the non-selective group (asterisks) and the selective group (plus signs) before the start of treatment. As already noted the slopes are similar. The P symbols plot the regression for QT/RR in the non-selective group on day 29 (52 hours after the last dose of drug). The slope has not changed, but at all heart rates QT is about 15 ms longer than before treatment. In contrast, on day 29 in the cardioselective group (A symbols) the slope is quite different ($p = 0{\cdot}02$) from that observed on day 1. In patients with higher rates QT was prolonged, but in the patients with slower rates, QT was actually shorter than at the start of treatment.

There was a similar difference between the groups on exercise. The regressions for QT/RR at the peak of the second exercise have been plotted in Fig. 3; asterisks and P symbols depict the plots for the non-selective group on day 1 and day 29, respectively, and the plus signs and A symbols represent the cardioselective group on days 1 and 29. For comparison with the regressions already given for day 1, the equations for day 29 are given in Table 6.

The conclusion to be drawn from these results was that though both groups were responding in a similar manner to the non-selective and cardioselective drugs in relation to the control of blood pressure, their adaptive responses were different in relation to heart rate and the QT/RR relation.

Table 6 *QT/RR regressions on day 29*

Rest		
Non-selective	(QT) = (RR) × 0·195 + 230	(r = 0·864)
Cardioselective	0·075 + 329	0·444
Exercise		
Non-selective	(QT) = (RR) × 0·238 + 183	(r = 0·773)
Cardioselective	0·125 + 263	0·470

Nevertheless there was a resting bradycardia in *some* patients in the non-selective group, though there was no statistically significant slowing of heart rate at rest on day 8 or 29 for the group as a whole. The patients were, therefore, divided, irrespective of drug taken, into those whose resting heart rate on day 29 had fallen by 10 per cent or more (heart rate responders) and those whose heart rate had not fallen or had, in some cases, actually risen a little (non-responders). The score for the heart rate responders according to the individual drugs was atenolol, 7/7; metoprolol, 6/9; propranolol 3/7; pindolol, 1/7; total 17/30.

For the heart rate responders, QT/RR regressions, at rest (asterisks) and during the second exercise (minus signs) before treatment are compared in Fig. 4 with similar regressions calculated on day 29 (plus signs, rest; dots, exercise). It appears that the patients who adapted to beta-blockade by a lowering of heart rate, also adapted by changing the relation between QT and RR (Table 7).

In contrast, a similar plot of the data from the 13 non-responders (Fig. 5) indicates that the QT/RR relation at rest on day 29 was identical to that observed on day 1, and was only slightly flattened during exercise on day 29. Perhaps the most striking feature of these plots was that whatever the QT/RR relation before treatment, by day 29 the QT/RR regressions had become very similar, irrespective of whether they were "heart rate responders" or not. The regression equations are shown in Table 7. For the heart rate responders, the QT/RR regression at rest was not quite significantly different on day 29 from that on day 1 (p=0·076), but during exercise the slope of the regression on day 29 was significantly different from that on day 1 (p=0·018). In contrast, for the non-responders, the slopes of the regression were already low on day 1, and had not altered significantly by day 29.

Comparison of Fig. 4 and 5, and the equations in Table 7 suggests that the "heart rate responders" might have constituted a different population *initially*, because the slopes of QT/RR regressions, both at rest and on exercise, were steeper in the

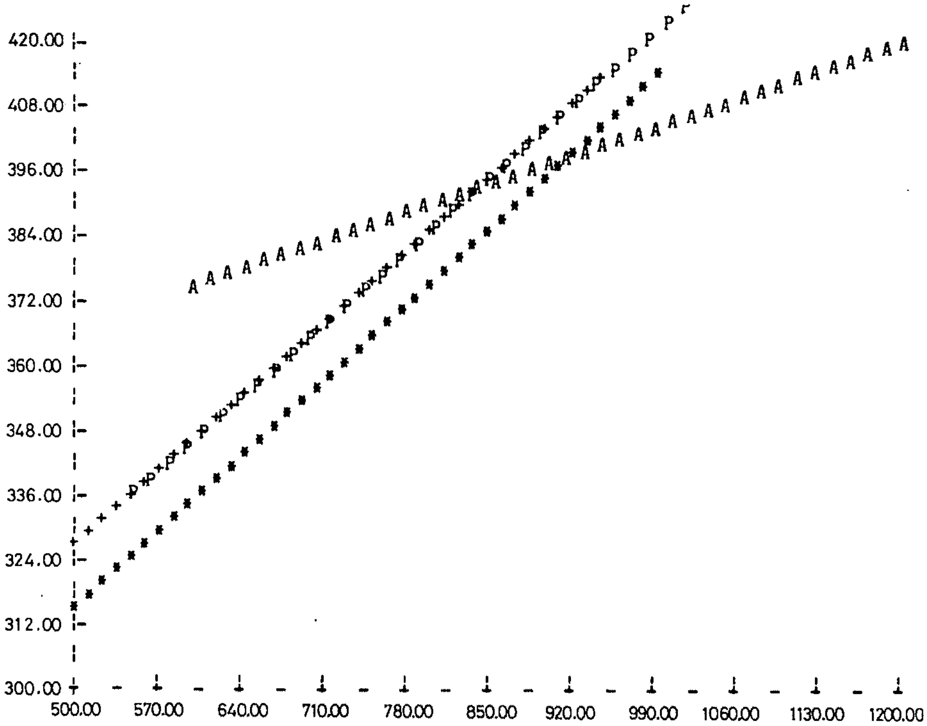

Fig. 2 *Adaptation of QT/RR relation at rest to treatment. Ordinate: QT, ms. Abscissa: RR, ms. Calculated linear regressions have been plotted of the QT/RR relation before treatment in the group on non-selective (asterisks) and cardioselective (plus signs) drugs. The regressions on day 29 are depicted by P symbols for the non-selective, and A symbols for the cardioselective group.*

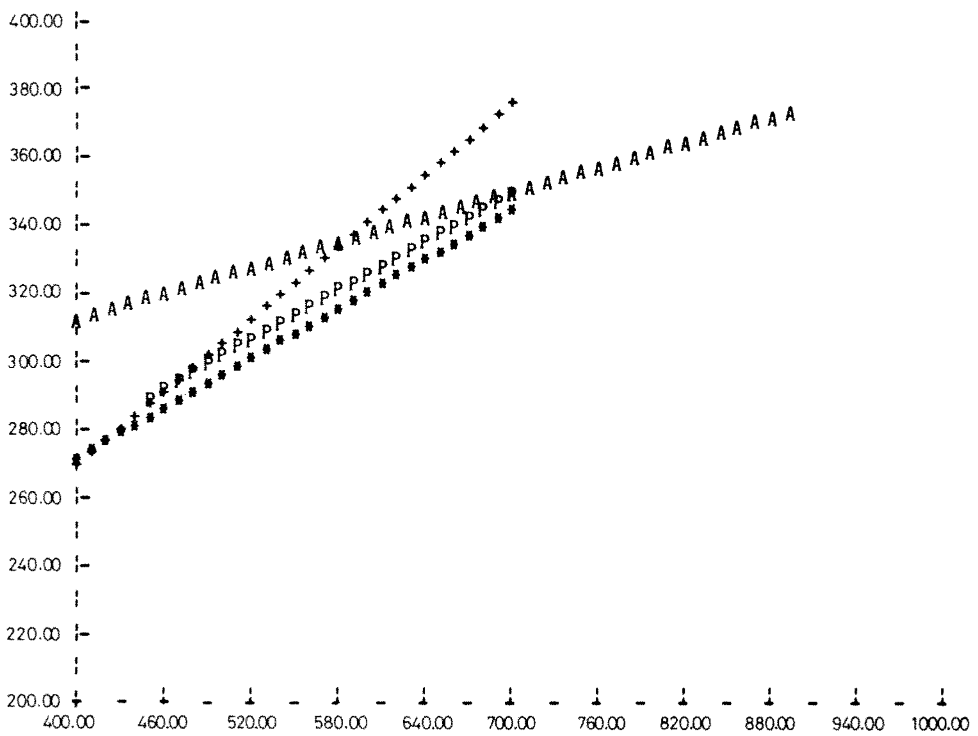

Fig. 3 *Adaptation of QT/RR relation on exercise. Ordinate: QT, ms. Abscissa: RR, ms. The calculated regressions of the QT/RR relation after the peak of the second exercise were steeper than at rest. Asterisks and P symbols, non-selective group on days 1 and 29, respectively. Plus signs and A symbols, cardioselective group on days 1 and 29.*

responders than in the non-responders. Though from Table 7 it is clear that the differences in these slopes were not statistically significant ($p = 0{\cdot}13$ at rest, and 0·077 on exercise), the p values were close enough to significance to suggest that this phenomenon, the QT/RR relation, would be worthy of further study in a subsequent investigation.

The question arose, therefore, whether there could have been some accidental bias in the blind assignment of patients, so that the higher proportion of heart rate responses in the cardioselective group might have been the result, not of a difference in the effect of the drugs, but of the inclusion of a larger number of "heart rate responders" in the groups assigned to the cardioselective compounds. Correlations were calculated between heart rate response and observations made before treatment and some of these are listed in Table 8.

Regression analysis was undertaken on the relation between the ultimate heart rate response against (a) initial resting heart rate ($r = 0{\cdot}29$), (b) initial increases in heart rate on exercise ($r = 0{\cdot}2$), and (c) initial QT_c ($r = 0{\cdot}17$), and several other

Table 7 *QT/RR relation in "heart rate responders" and non-responders on days 1 and 29*

	Slope	*Intercept*	*Correlation coefficient*
Day 1			
Rest: Responders	0·236	198	0·697
Non-responders	0·139	266	0·654
Significance of difference in slopes Responders/non-responders	p=0·13		
Exercise 2: Responders	0·346	130	0·891
Non-responders	0·217	194	0·769
Significance of difference in slopes Responders/non-responders	p=0·077		
Day 29			
Rest: Responders	0·127	285	0·654
Non-responders	0·126	282	0·537
Exercise 2: Responders	0·150	242	0·519
Non-responders	0·158	237	0·534

Significance of difference between slopes for QT/RR regressions.
Responders: day 1 compared with day 29. Rest: p=0·076
Second exercise: p=0·018
Non-responders: day 1 compared with day 29.
Rest: p=0·87
Second exercise: p=0·52.

Table 8 *Comparison of initial data*

	Responders	*Non-responders*	*Difference*	*p value*
Initial heart rate	90·5 ±3·8	82·9 ±3·5	7·6	0·16
Initial increase in heart rate on exercise	48·1 ±4·9	40·9 ±3·8	7·2	0·28
Initial QTc	0·436 ±0·008	0·431 ±0·008	0·005	0·6

initial measurements, but no significant correlations were found. It was concluded, therefore, that the bradycardia observed at rest on day 29 in the cardioselective group was indeed the result of an adaptation to the treatment, and that the order of potency in causing adaptive bradycardia at rest was atenolol >metoprolol >propranolol >pindolol. On day 29 in four of seven patients on pindolol, heart rate at rest was actually a little faster than on day 1.

(6) EFFECT OF ACUTE INTRAVENOUS BLOCKADE ON THE QT/RR RELATION

Increases in heart rate on exercise were reduced by acute intravenous beta-blockade. When QT was plotted against RR for observations obtained in the period after injection, both at rest and during exercise, the regression became flatter, that is QT interval became less closely related to heart rate. This was very similar to the adaptation after prolonged treatment observed in the absence of the drug. This less steep relation between QT and heart rate after intravenous beta-blockade did not alter significantly during treatment. For comparison with the figures given above, the equations after acute blockade are given in Table 9.

(7) LACK OF CORRELATION BETWEEN BRADYCARDIA AND CONTROL OF BLOOD PRESSURE

Both bradycardia and reduction of hypertension may persist after stopping treatment after prolonged

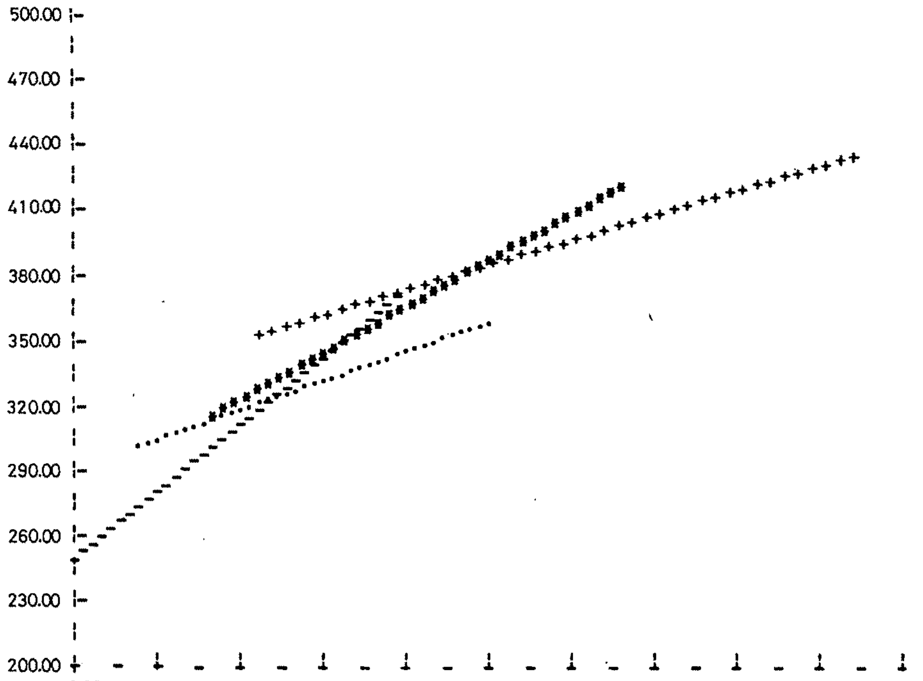

Fig. 4 *QT/RR relation before treatment in patients who ultimately had an adaptive bradycardia during treatment. Ordinate: QT, ms. Abscissa: RR, ms. The calculated regression of the "heart rate responders" is plotted at rest (asterisks) and at the peak of the second exercise (minus signs) on day 1, and at rest (plus signs) and on exercise (dots) on day 29. At rest, the difference in slopes on days 1 and 29 was not quite significant (p=0·076), but on exercise the slope on day 29 was significantly different from that on day 1 (p=0·018) (see Table 7).*

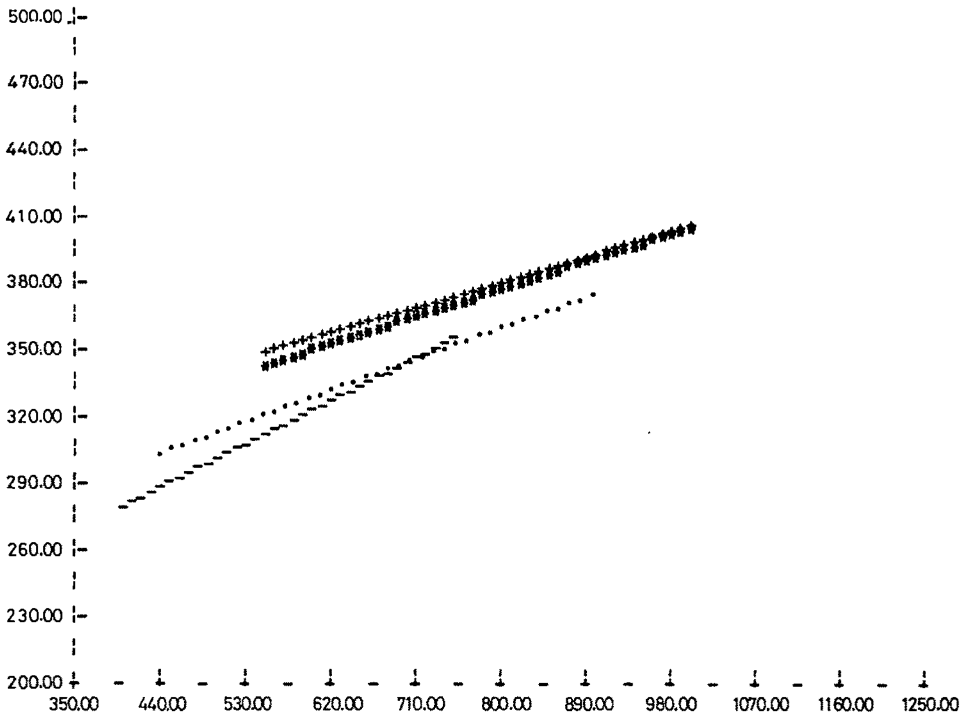

Fig. 5 *Non-responders. The QT/RR regression at rest on day 1 (asterisks) was the same as on day 29 (plus signs). On exercise, the slope of the regression on day 29 (dots) was less steep than on day 1 (minus signs) (that is a change in the same direction as that exhibited by heart rate responders), but the slopes were not, in fact, significantly different (see Table 7).*

beta-blockade, and it might be thought that patients who are adapters in the one respect, might also be adapters in the other. Fig. 6 indicates that this is not the case. Changes in heart rate have been plotted against changes in diastolic blood pressure at day 29, for all patients. Heart rate responders (HR change >10%) are denoted by R, and non-responders by N. The correlation coefficient for all patients was 0·108, for responders 0·092, and for non-responders 0·038.

(8) TIME COURSE OF DEVELOPMENT OF HYPOTENSIVE RESPONSE TO TREATMENT AND OF ADAPTIVE RESPONSE

(A) *Hypotensive response to treatment*

In estimating the response of hypertensives to treatment with beta-blockers, blood pressure is normally measured while patients are still taking the drugs. By this criterion all patients "responded", in that, by the 70th day of treatment, there was no patient on any drug whose diastolic pressure was not lower than on admission to the trial, and only one (on metoprolol) in whom this fall did not exceed 5 mmHg. There were, however, two patients on pindolol, and one each on propranolol and atenolol, in whom diastolic pressure had not fallen by the 42nd day of treatment, and in these four individuals systolic pressure had not fallen even by the 70th day. On the 16th day the "non-responder" scores were, for atenolol and pindolol, one each for both diastolic and systolic pressures; for propranolol, three for diastolic, two for systolic; and for metoprolol, three for diastolic, four for systolic.

Table 9 *Effect of acute beta-blockade on the QT/RR regression*

At rest after intravenous beta-blockade			
Non-selective	Day 1	(QT)=(RR)×0·131+270·2	r=0·581
	Day 29	0·150+260·4	0·736
Cardioselective	Day 1	0·102+296·9	0·485
	Day 29	0·092+327·5	0·465
During second exercise after intravenous beta-blockade			
Non-selective	Day 1	(QT)=(RR)×0·178+215·2	r=0·784
	Day 29	0·232+186·9	0·882
Cardioselective	Day 1	0·206+210·6	0·703
	Day 29	0·170+238·9	0·685

(B) *Adaptation*

An adaptive response to treatment may be defined as a lowered blood pressure persisting after withdrawal of treatment, at a time when no significant concentration of the drug remains in the body. Obviously this cannot be estimated at the same time as the response to treatment already described. By this criterion, on day 29, for diastolic pressure, there were two adapters on propranolol, four on pindolol, five on metoprolol, and six on atenolol, a total of 17/30, but these patients were not, of course, as already shown in Fig. 6, the same 17 who showed an adaptive bradycardia. For systolic pressure, adaptation was present on day 29 in six patients each on metoprolol and atenolol, in four on pindolol, and in five on propranolol. The scores were almost identical on day 8, indicating that in those patients who adapt, the adaptation occurs quite early, though it may progress further during treatment. There were insufficient patients for a full quantitative analysis to have been worth while, but the time-course of the development of adaptation seems to merit further study.

Discussion

Experimental work in animals has shown that prolonged treatment with doses of beta-blockers equivalent to those used clinically induces profound adaptive readjustments which include a decrease in peripheral sympathetic background activity,[30] and a lengthening of cardiac action potential duration. Such changes long outlast the end of treatment. In man, the hypotensive effect of beta-blockers does not develop optimally for days or weeks, and the implication is that some sort of adaptation to repeated interference with the sympathetic control of the heart is involved. The problem has been to identify the site at which such an adaptation occurs, and there have been no lack of candidates. The myocardium, the arterioles, the baroreceptors, the brain, the renin-angiotensin system, and the peripheral sympathetic have all had their advocates.

The present study was designed to distinguish adaptive changes, induced by prolonged beta-blockade and persisting when the drugs had been eliminated from the body, from the immediate

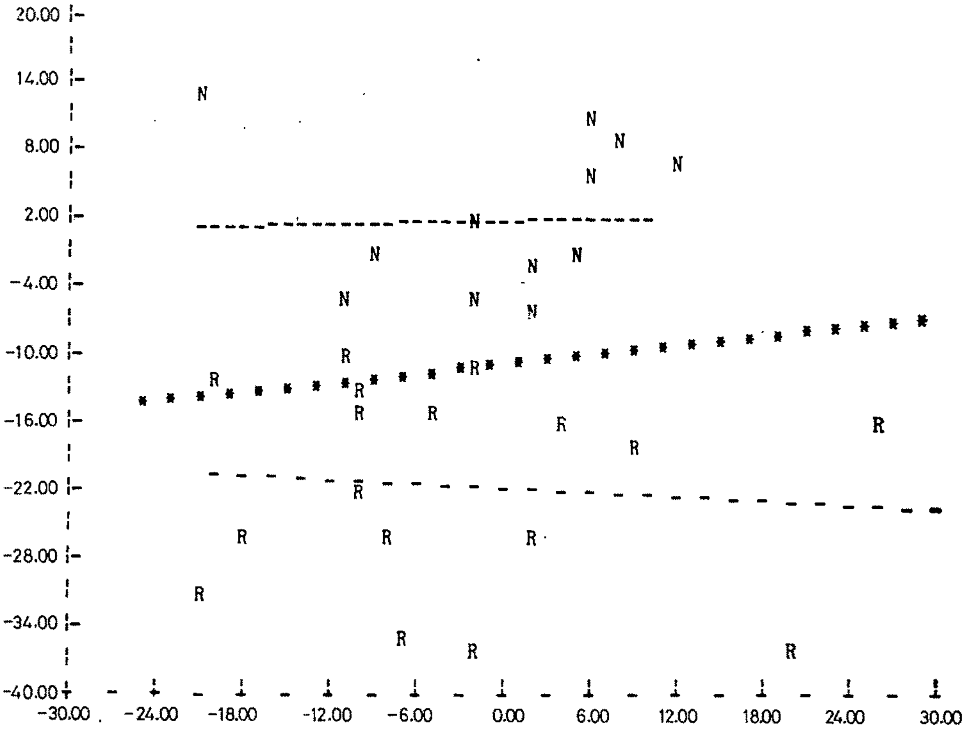

Fig. 6 *Absence of correlation between adaptive bradycardia and control of blood pressure. Ordinate: percentage change in heart rate at rest on day 29. Abscissa: percentage change in diastolic blood pressure on day 29. R=patients with a bradycardia greater than 10 per cent (heart rate responders). N=non-responders. The minus signs shown least squares fits to the R (r=0·092) and N (r=0·038) points, and the asterisks give the fit for all results (r=0·108).*

effects of the drugs themselves. There was no evidence, 52 hours after the last dose of drug, of the development of any "supersensitivity". In no patient in the cardioselective group was the resting heart faster than before treatment, but in four of seven patients on pindolol heart rate was up by 1·6, 6, 12, and 13 per cent, a change that may be related to the intrinsic sympathomimetic activity of this compound. In 17 of 30 patients heart rate at rest was slower by a margin of more than 10 per cent. Furthermore, the peak heart rates on exercise were also lower in both groups. There was no evidence of a "rebound" of blood pressure 52 hours after withdrawal of treatment.

Brundin *et al.*[27] reported that in eight hypertensives treated with propranolol for two months or more, and examined 72 hours after the last oral dose, effects remaining after withdrawal of the drug could be detected—"the persistent effects appeared as: (1) a considerable reduction of heart rate (2) an almost total lack of acute haemodynamic response to intravenous propranolol administration". In our study, though a persistent bradycardia ($>10\%$) was observed in all seven patients on atenolol, and in six of nine on metoprolol, it was found in only three of seven patients on propranolol. No significant adaptive changes in the response to acute intravenous administration of any of the drugs used were observed, either in heart rate or blood pressure responses.

In the present investigation the doses used were adjusted in an attempt to produce what was regarded as a satisfactory response to treatment, that is to say a reduction of diastolic pressure to approximately 90 mmHg (11·97 kPa). As already noted, however, there were a few patients in each group in whom the control of hypertension was minor (fall of less than 10 mmHg systolic or 5 mmHg diastolic). It is possible, of course, that further treatment beyond the limit of this trial would have ultimately improved the response. Regression analysis indicated that there was no correlation at all between the adaptive response of the blood pressure to treatment and the adaptive changes in resting heart rate ($r=0{\cdot}1$ for all patients).

The adaptation to treatment with beta-blockers involved a less steep relation between heart rate and QT interval. The traditional correction derived from the work of Bazett,[29] $QT_c=QT/\sqrt{RR}$ measured in seconds, resulted in a wide range of QT_c values in the patients before the start of treatment. Recently, Milne *et al.*[31] have questioned the appropriateness of the Bazett correction. Extensive statistical analyses indicated that a linear regression of QT/RR gave as good (or as bad) a fit as $QT/\sqrt{RR}$ or polynomial regressions. It was apparent that with all the drugs the correlation between QT and RR was diminished during treatment, and was also reduced by acute beta-blockade even before the treatment started.

The questions remain how these results may be explained, and whether they have any clinical significance. The QT interval measures the time between the beginning and the end of the flow of ventricular current in the axis of the recording electrodes; that is, from depolarisation of the first to repolarisation of the last cell. It does not, therefore, measure action potential duration, but contains within it a variety of disparate individual action potential durations and can also be altered by changes in conduction pathway. A lengthening of QT can only be taken to measure prolongation of action potential duration if the latter is uniform, and if conduction is unchanged. Action potential duration itself can be interpreted in terms of mathematical equations involving time and voltage-dependent ionic conductances, but the applicability of such models to cardiac muscle is dubious for two main reasons. First, the experimental data put into the equations are suspect, because membrane voltages assumed to be uniform are not, in fact, uniformly distributed even in Purkinje fibres, much less in ventricular muscle, and the injected currents themselves not only control the membrane voltages (the desirable effect), but also alter the extracellular ionic concentrations, an undesirable effect, because it is upon the constancy of these concentrations that the validity of the calculations is based.

Such technical matters have been discussed in detail elsewhere,[32] but there is a second more fundamental reason for doubting whether the cardiac action potential can be assumed to be determined solely by conductances through voltage and time-dependent channels analogous to those of nerve. Cardiac muscle fibres are of small diameter (atrial 6 to 8 μ, ventricular 10 to 15 μ),[33] and 35 to 40 per cent of the intracellular volume is occupied by mitochondria. The surface to volume ratio is high, and the energy turnover is rapid: "passively" determined membrane conductance changes can be overridden by metabolic control. Action potential duration is rapidly and dramatically shortened by hypoxia or ischaemia, and this effect is exacerbated by fatty acids[34] or ameliorated by glucose.[35] Action potential duration is also shortened in hyperthyroidism,[36] or by beta-adrenergic stimulation, and is lengthened by hypothyroidism, or certain drugs.[37 38] In contrast to these major effects on action potential duration, the changes produced in intracellularly recorded action potential duration *in vitro* by large alterations in pacing frequency are minor, two or three milliseconds only.[39]

If such considerations are applicable to man, QT interval in the short term would be controlled by two main influences. The first, a comparatively small "biophysical" effect, would be the heart rate; the second would be changes in the concentration of intracellular metabolities, subject to control by beta-receptor agonists, substrate availability, etc. The clinical validity of this hypothesis can be tested. For example, changes in heart rate produced by pacing should cause less shortening of QT than comparable changes induced by the natural agonist, noradrenaline, released from nerve endings during exercise. Conversely, in patients with fixed-frequency pacemakers, QT should shorten during exercise in spite of the absence of any change of heart rate. The flattening of the QT/RR relation, after acute intravenous blockade, and as an adaptation to prolonged treatment, could thus be explained as a reduction of the "metabolic" control of action potential duration, the more important of the two. We found in our hypertensive patients no evidence that prolonged beta-blockade induced any supersensitivity to adrenergic stimulation, such as has been described in human volunteers.[40]

An adaptive bradycardia (>10%) occurred in 17 of 30 of our patients. In this group of "heart rate responders" the QT/RR relation appeared to be somewhat steeper before treatment than in the non-responder group. Though not statistically significant in this study, the difference was so close to significance ($p=0{\cdot}13$ at rest, and 0·077 on exercise) as to suggest that this phenomenon would be worth looking at again in a prospective trial, in an attempt to identify probable responders before the start of treatment. Such identification would not, of course, be of help in the treatment of hypertensives, since there was no correlation between heart rate response and blood pressure control, but it could be useful in the selection for treatment with beta-blockers of anginal patients, for whom bradycardia may be of greater therapeutic significance.

References

1 Prichard BNC. Hypotensive action of pronethalol. *Br Med J* 1964; **i:** 1227–8.

2 Prichard BNC, Gillam PMS. Use of propranolol (Inderal) in treatment of hypertension. *Br Med J* 1964; **ii:** 725–7.

3 Humphreys GS, Delvin DG. Ineffectiveness of propranolol in hypertensive Jamaicans. *Br Med J* 1968; **ii:** 601–3.

4 Zacharias FJ, Cowen KJ. Controlled trial of propranolol in hypertension. *Br Med J* 1970; **i:** 471–4.

5 Zacharias FJ. Propranolol in hypertension: a 5-year rabbits. *Br J Pharmacol* 1980; **68:** 363–71.

6 Prichard BNC, Boakes AJ, Day G. Practolol in the treatment of hypertension. *Postgrad Med J* 1971; **47,** suppl: 84–92.

7 Lund-Johansen P. Haemodynamic consequences of long-term beta-blocker therapy: a 5-year follow up study of atenolol. *J Cardiovasc Pharmacol* 1979; **1:** 487–95.

8 Tarazi RC, Dustan HP. Beta adrenergic blockade in hypertension. *Am J Cardiol* 1972; **29:** 633–40.

9 Hansson L, Zweifler AJ, Julius S, Hunyor SN. Hemodynamic effects of acute and prolonged β-adrenergic blockade in essential hypertension. *Acta Med Scand* 1974; **196:** 27–34.

10 Franciosa JA, Freis ED. Normal cardiac output during beta-blockade with Timolol in hypertensive patients. *Clin Pharmacol Ther* 1975; **18:** 158–64.

11 Atterhøg J-H, Dunér H, Pernow B. Haemodynamic effects of pindolol in hypertensive patients. *Acta Med Scand* 1977; suppl 606: 55–62.

12 Reybrouck T, Amery A, Billiet L. Hemodynamic response to graded exercise after chronic beta-adrenergic blockade. *J Appl Physiol* 1977; **42:** 133–8.

13 Bühler FR, Laragh JH, Baer L, Vaughan ED Jr, Brunner HR. Propranolol inhibition of renin secretion. *N Engl J Med* 1972; **287:** 1209–14.

14 Michelakis AM, McAllister RG. The effect of chronic adrenergic receptor blockade on plasma renin activity in man. *J Clin Endocrinol Metab* 1972; **34:** 386–94.

15 Esler MD, Nestel PJ. Evaluation of practolol in hypertension. *Br Heart J* 1973; **35:** 469–74.

16 Castenfors J, Johnsson H, Orö L. Effect of alprenolol on blood pressure and plasma renin activity in hypertensive patients. *Acta Med Scand* 1973; **193:** 189–95.

17 Stokes GS, Weber MA, Thornell IR. β-blockers and plasma renin activity in hypertension. *Br Med J* 1974; **i:** 60–62.

18 Bravo EL, Tarazi RC, Dustan HP. β-adrenergic blockade in diuretic-treated patients with essential hypertension. *N Engl J Med* 1975; **292:** 66–70.

19 Lewis PJ, Haeusler G. Reduction in sympathetic nervous activity as a mechanism for hypotensive effect of propranolol. *Nature* 1975; **256:** 440.

20 Prichard BNC, Gillam PMS. Treatment of hypertension with propranolol. *Br Med J* 1969; **i:** 7–16

21 Vaughan Williams EM. Adaptation of the heart and sympathetic system to prolonged adrenoceptor blockade. *Proc R Soc Med* 1977; **70,** suppl 11: 49–62.

22 Vaughan Williams EM, Raine AEG, Cabrera AA, Whyte JM. The effects of prolonged β-adrenoceptor blockade on heart-weight and cardiac intracellular potentials in rabbits. *Cardiovasc Res* 1975; **9:** 579–92.

23 Florio RA, Nayler WG, Slade A, Vaughan Williams EM, Yepez CE. Effect of prolonged β-adrenoceptor blockade on heart weight and ultrastructure in young rabbits. *Br J Pharmacol* 1980; **68:** 363–71.

24 Raine AEG, Pickering TG. Cardiovascular and sympathetic response to exercise after long-term beta-adrenergic blockade. *Br Med J* 1977; **ii,** 90–92.

25 Littler WH, Honour AJ, Sleight P, Stott FD. Continuous recording of direct arterial pressure and

electrocardiogram in unrestricted man. *Br Med J* 1972; **3:** 76–78.

26 Brown HC, Carruthers SG, Johnston GD, *et al.* Clinical pharmacological observations on atenolol, a beta-adrenoceptor blocker. *Clin Pharmacol Ther* 1976; **20:** 524–34.

27 Brundin T, Edhag O, Lundman T. Effects remaining after withdrawal of long-term beta-receptor blockade. *Br Heart J* 1976; **38:** 1065–72.

28 Raine AEG, Vaughan Williams EM. Adaptation to prolonged beta-adrenoceptor bockade in young and adult rabbits. *Br J Pharmacol* 1980 In press.

29 Bazett HC. An analysis of the time relations of electrocardiograms. *Heart (Lond)* 1920; **7:** 353–70.

30 Raine AEG, Chubb IW. Long-term β-adrenergic blockade reduces tryosine hydroxylase and dopamine β-hydroxylase activities in sympathetic ganglia. *Nature* 1977; **267:** 265–7.

31 Milne JR, Camm AJ, Ward DE, Spurrell RAJ. Effect of intravenous propranolol on QT interval. A new method of assessment. *Br Heart J* 1980; **43:** 1–6.

32 Vaughan Williams EM. *Antiarrhythmic action.* London: Academic Press.

33 Legato MJ. Ultrastructure of the atrial, ventricular and Purkinje cell, with special reference to the genesis of arrhythmias. *Circulation* 1973; **47:** 178–89.

34 Cowan JC, Vaughan Williams EM. The effects of palmitate on intracellular potentials recorded from Langendorff-perfused guinea-pig hearts in normoxia and hypoxia, and during perfusion at reduced rate of flow. *J Mol Cell Cardiol* 1977; **9:** 327–42.

35 McDonald TF, MacLeod DP. Metabolism and the electrical activity of anoxic ventricular muscle. *J Physiol (Lond)* 1973; **229:** 559–82.

36 Freedberg AS, Papp J Gy, Vaughan Williams EM. The effect of altered thyroid state on atrial intracellular potentials. *J Physiol (Lond)* 1970; **207:** 357–70.

37 Singh BN, Vaughan Williams EM. The effect of amiodarone, a new anti-anginal drug, on cardiac muscle. *Br J Pharmacol* 1970; **39;** 657–67.

38 Singh BN, Vaughan Williams EM. A third class of anti-arrhythmic action. Effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle, of MJ 1999 and AH 3474. *Br J Pharmacol* 1970; **39:** 675–87.

39 Vaughan Williams EM. A study of intracellular potentials and contractions in atria, including evidence for an after-potential. *J Physiol (Lond)* 1959; **149:** 78–92.

40 Ross PJ, Lewis MJ, Henderson AH. Heart rate responses after beta-blocker withdrawal (abstract). *Br Heart J* 1980; **43:** 114–5.

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Br Heart J 1980; **44:** 488–98

Effects of propranolol on myocardial oxygen consumption, substrate extraction, and haemodynamics in hypertrophic obstructive cardiomyopathy

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SUMMARY Myocardial substrate extraction, coronary sinus flow, cardiac output, and left ventricular pressure were measured at increasing pacing rates before and after propranolol (0·2 mg/kg) in 13 patients with hypertrophic obstructive cardiomyopathy (HOCM) during diagnostic cardiac catheterisation. At the lowest pacing rate myocardial oxygen consumption varied considerably between patients and very high values were found in several individuals (range 10·1 to 57·5 ml/min). These large differences between patients were not explicable by differences in cardiac work; consequently, cardiac efficiency, estimated from the oxygen cost of external work, varied between patients and was lower than normal in all but two. The pattern of substrate extraction at the lowest pacing rate was similar to results reported for the normal heart, and measured oxygen consumption could be accounted for by complete oxidation of the substrates extracted; thus there was no evidence of a gross abnormality of oxidative metabolism, suggesting that low efficiency lay in the utilisation rather than in the production of energy. Each of the four patients with the highest myocardial oxygen consumption and lowest values of efficiency sustained progressive reductions in lactate and pyruvate extraction as heart rate increased, and at the highest pacing rate had low ($<3\%$) or negative lactate extraction ratios. In three of these four, coronary sinus flow did not increase progressively with each increment in heart rate. One patient with low oxygen consumption and normal efficiency also failed to increase coronary flow with the final increment in heart rate, and produced lactate at the highest pacing rate. Thus the five patients in whom pacing provoked biochemical evidence of ischaemia all had excessive myocardial oxygen demand and/or limited capacity to increase coronary flow. Propranolol did not change lactate extraction significantly at any pacing rate in either the ischaemic or non-ischaemic groups. In only one patient was ischaemia at the highest pacing rate abolished after propranolol, and this was associated with a 30 per cent reduction in oxygen consumption. These results do not demonstrate a direct effect of propranolol upon myocardial metabolism in patients with HOCM, but emphasise the potential value of beta-blockade in protecting these patients from excessive increases in heart rate.

Angina pectoris is a common symptom in patients with hypertrophic obstructive cardiomyopathy (HOCM),[1 2] suggesting that the oxygen demand of the hypertrophied heart may exceed the capacity of the coronary circulation to supply it. The occurrence of angina is not related to the severity of obstruction,[3] implying that high myocardial oxygen demand secondary to increased left ventricular work is not the usual mechanism of ischaemia. The severity of hypertrophy is out of proportion to the increase in cardiac work that would be needed to overcome obstruction[4]; this inappropriate increase in muscle mass may lead to increased myocardial oxygen demand which is excessive when considered in relation to the external work performed by the heart. In the presence of severe hypertrophy resulting from aortic stenosis, coronary flow is unable to increase when the heart is stressed[5]; thus in addition to increasing oxygen demand,

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hypertrophy may limit the ability of the coronary vasculature to increase oxygen delivery.

Propranolol has been used extensively in the treatment of patients with HOCM, and has been shown to improve angina,[6 7] reduce the outflow tract gradient,[8] and increase left ventricular diastolic distensibility.[9] Its beneficial effect upon angina may be because of reduction of heart rate on exercise, but recent studies in patients with coronary artery disease have suggested that beta-blockade may improve myocardial ischaemia even when heart rate is controlled by pacing.[10 11]

In this report we present the results of studies upon myocardial metabolism, coronary flow, and haemodynamics at increasing heart rates in patients with HOCM, with particular reference to the factors contributing to the development of metabolic evidence of ischaemia. In addition, the effects of propranolol administration were studied to determine whether or not this drug has beneficial actions that are independent of heart rate.

Patients and methods

Thirteen patients (age 18 to 62) were studied. All were symptomatic and were undergoing diagnostic cardiac catheterisation for suspected HOCM. The patients gave written consent and the Hospital Ethical Committee approved the study.

Beta-blocking drugs were stopped two days before catheterisation. All studies were performed in the morning after an overnight fast. Atropine 0·3 mg and diazepam 10 mg intramuscularly and heparin 45 units/kg intravenously were given one hour before catheterisation. Pretreatment with heparin has been shown to minimise the effect of a subsequent dose upon arterial free fatty acid concentration.[12] Right and left heart catheterisation were performed via the right femoral vein and artery. A second dose of heparin was given immediately after arterial catheterisation. In four patients transseptal puncture was performed and the outflow gradient demonstrated by simultaneous measurement of left ventricular body pressure via the transseptal catheter and outflow pressure via the arterial catheter. In the other patients gradients were measured by withdrawal of an end-hole catheter from the ventricular apex to the aorta, and then confirmed by a twin lumen catheter. Inhalation of amyl nitrate was used to provoke a gradient when appropriate.

Using the long sheath technique[13] the left heart catheter was replaced by a catheter tip micromanometer (Telco MM52, or Millar) which was positioned in the body of the left ventricle. The right heart catheter was replaced by a Schwarzer Swan Ganz fibreoptic catheter which was advanced to the pulmonary artery for measurement of cardiac output. Via a left antecubital vein a Ganz pacing and thermistor catheter was advanced into the coronary sinus. Its site was confirmed by injection of contrast medium, and infusion of cold saline into the right atrium.[14] Coronary sinus pacing was established just above basal heart rate. Cardiac output, left ventricular pressure, and coronary sinus flow were measured, and left ventricular and coronary sinus blood sampled simultaneously. The procedure was repeated at three or four pacing rates. Pacing was stopped, and propranolol 0·2 mg/kg given intravenously. Twenty minutes later the outflow gradient was measured at basal heart rate, and then the pacing study repeated. Biplane left ventricular cineangiography was performed at the end of the study. In nine patients the left anterior oblique view with simultaneous hand injection into the right ventricle was used to define septal hypertrophy.[15] Selective coronary arteriography was performed in 12 patients.

The micromanometer and thermistor signals were displayed on a Cambridge 12 channel recorder and stored on tape. The pressure signal was differentiated, and KV_{max} derived from developed pressure.[16] Mean systolic pressure was estimated by planimetry of the left ventricular pressure trace and used in the calculation of systolic pressure time index and left ventricular minute work. Green dye curves obtained in the pulmonary artery were analysed by an IVH 3 Schwarzer cardiac output computer. Coronary sinus blood flow was measured by constant infusion thermodilution.[17]

Blood samples were added to an aliquot of 10 per cent perchloric acid for deproteinisation and subsequent determination of lactate and pyruvate,[18] hydroxybutyrate and acetoacetate,[19] and glycerol.[20] For measurement of free fatty acids[21] blood was added to sequestrene tubes and centrifuged. All samples were put on ice, and then stored at −20°C. Heparinised samples were taken for determination of oxygen content upon a LEX-0_2 CON-TL.

Extraction of a substrate is defined as the difference in concentration between arterial and coronary sinus blood (A − V), and extraction ratio is that difference as a percentage of arterial concentration (A − V/A%). Oxygen extraction ratio of a substrate is defined as the amount of oxygen required to catabolise completely the amount of that substrate extracted, expressed as a percentage of the total oxygen extracted by the heart. For example, one mole of lactate requires three mole of oxygen. Thus the amount of oxygen needed to catabolise extracted lactate can be calculated, and expressed as a percentage of the total oxygen extracted by the heart. Myocardial oxygen consumption is calculated as the difference between arterial and coronary sinus oxygen consumption (A − V) multiplied by coronary sinus flow. Myocardial efficiency is estimated by the formula of Bing and Michal[22] where

$$\text{efficiency} = \frac{\text{Left ventricular minute work (kg m/min)}}{\text{Myocardial } O_2 \text{ consumption (ml/min)} \times 2{\cdot}059 \times 0{\cdot}806}\ \%$$

Statistical analysis was performed using Student's t test, paired t test, and linear regression. A value of $p < 0{\cdot}05$ was considered significant. Values are expressed as mean ± standard error of the mean.

Results

The clinical details of the 13 patients are listed in Table 1. Twelve complained of exertional dyspnoea, and eight of angina pectoris. All had physical signs suggestive of HOCM. One patient (case 9) had auscultatory and echocardiographic signs of mitral stenosis found at catheter to be trivial (Gorlin valve area 3·3 cm^2); this patient's aortic valve was normal.

At basal heart rate the mean left ventricular outflow gradient was 43·9 mmHg before, and 35·9 mmHg after propranolol (NS). In case 13, no gradient was present at rest, but inhalation of amyl nitrate provoked an outflow gradient of 13 mmHg.

Angiographic assessment of the severity and distribution of hypertrophy showed it to be limited to the septum in seven patients, with hypertrophy of both septum and free wall in six. The coronary arteries were normal in 12 patients (as judged from coronary arteriography in 11, and aortography in one). Minor irregularities but no critical stenoses were seen in case 4 on coronary arteriography.

METABOLIC RESULTS

Arterial lactate concentration was 0·474 ± 0·02 mmol/l before and 0·496 ± 0·02 mmol/l after propranolol (NS). Fig. 1 shows myocardial lactate extraction ratio at each pacing rate. Before propranolol mean lactate extraction ratio fell from 37·4 per cent ± 3·1 at the lowest pacing rate to 9·1 per cent ± 7·8 at the highest pacing rate. This fall was largely because of five patients in whom lactate extraction fell progressively as heart rate increased. At the highest pacing rate the mean lactate extraction ratio of these five patients was −11·8 per cent (range 2·7 to −33·4%), and three of them experienced angina. Lactate extraction ratio remained high in the other eight patients at all pacing rates, and the difference between the two groups was significant at the second, third, and fourth pacing rates. After propranolol, lactate extraction did not change significantly at any heart rate in either group of patients. Only one of the five

Table 1 *Clinical and haemodynamic details of patients*

Case no.	*Age*	*Sex*	*Symptoms*				*Resting gradient*		*Distribution of hypertrophy*	*Mitral ** regurgitation*	*Myocardial efficiency at first pacing rate (%)*	
			Dyspnoea	*Angina*	*Palpitation*	*Syncope*	*Control*	*Propranolol*			*Control*	*Propranolol*
1	41	M	+	0	+	0	27	13	Septum and moderate generalised	I	22·7	9·1
2	58	M	+	+	+	0	26	47	Septum	0	15·9	20·2
3	42	F	+	0	+	0	65	48	Septum	I	22·3	23·7
4	62	M	+	0	+	+	38	35	Mid septum	0	38·6	33·1
5	24	M	+	0	0	0	70	11	Septum	II	20·3	—
6	42	M	+	+	+	0	49	36	Septum	0	23·4	13·9
7	26	M	+	+	+	0	22	12	Septum	0	22·7	22·1
8	39	M	+	+	+	0	5	0	Septum and moderate generalised	I	24·4	26·2
9*	53	F	+	+	0	0	100	91	Septum	II	40·3	28·3
10*	18	F	+	+	0	0	27	26	Massive septal and severe generalised	II	6·1	6·3
11*	29	F	+	+	+	0	69	36	Septal and moderate generalised	II	10·4	13·0
12*	23	F	+	+	+	0	61	100	Septal and severe generalised	II	12·0	11·9
13*	28	M	0	0	+	+	0	0	Generalised	0	14·4	17·8
							Mean 43 ±9	35 ±9			Mean 21·5 ±2·7	19·7 ±2·2
							NS				NS	

*Patients who developed abnormal lactate extraction at the highest pacing rate.
**Mitral regurgitation, grade 0 = none, I = mild, II = moderate, III = severe, IV = very severe.

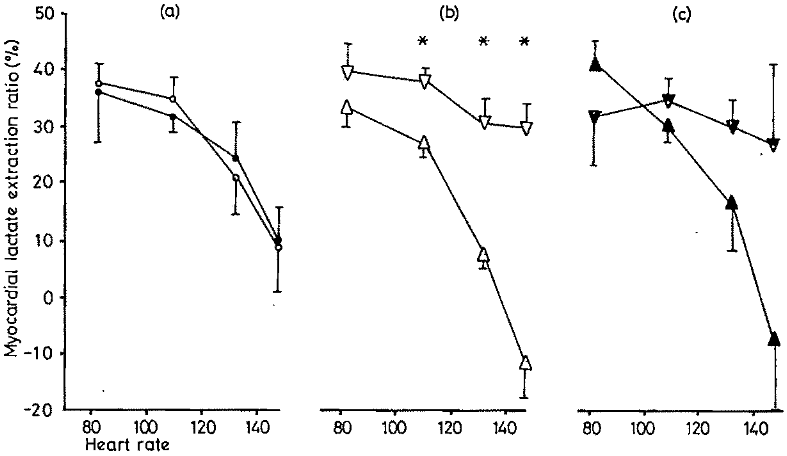

Fig. 1 *Myocardial lactate extraction ratio at each pacing rate.* (a) *Mean* ±*SEM of all patients. Open circles, before propranolol; closed circles, after propranolol.* (b) *Separation of the two groups on the basis of lactate extraction ratio at the highest pacing rate before propranolol.* △ *mean* ±*SEM of the five patients who had low or negative extraction ratios at highest pacing rate.* ▽ *mean* ±*SEM of the remaining patients. Lactate extraction ratio was significantly lower in these five patients than in the others at all but the first pacing rate.* (c) *Comparison of the two groups after propranolol. Differences between the two groups were no longer significant; however, mean extraction ratio did not change significantly in either group at any heart rate (*p < 0·5).*

patients with low extraction (case 12) showed distinct improvement after the drug, 43·8 per cent compared with 2·7 per cent at the highest pacing rate, and this was associated with relief of angina.

Arterial pyruvate concentration was 0·036 ± 0·002 mmol/l both before and after propranolol. Considering all pacing rates together, extraction was related to arterial concentration before and after the drug ($r = 0{\cdot}88$, $p < 0{\cdot}01$; $r = 0{\cdot}76$, $p < 0{\cdot}01$). Before propranolol pyruvate extraction ratio fell from 31·8 per cent ±5 to 20·6 per cent ±4·5 between the highest and lowest pacing rates (Fig. 2). This reduction was the result of the behaviour of the five patients with abnormal lactate extraction. Their pyruvate extraction ratios fell progressively as heart rate increased, while extraction remained high at all heart rates in the other eight patients, and the difference between the two groups was significant at the second, third, and fourth pacing rates. After propranolol, the pyruvate extraction ratio did not change significantly.

Arterial concentration and extraction of hydroxy-

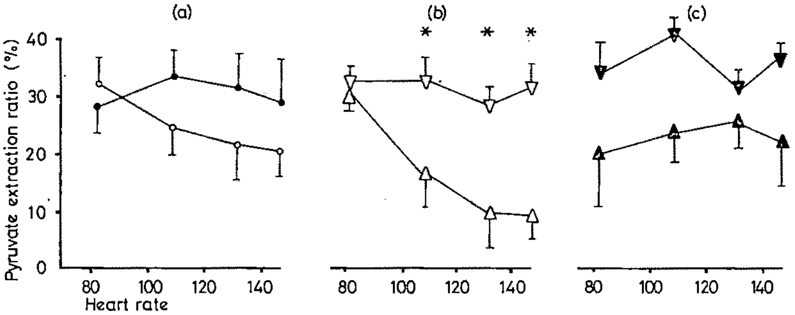

Fig. 2 *Pyruvate extraction ratio at each pacing rate.* (a) *Mean*±*SEM of all patients: open circles, before propranolol; closed circles, after propranolol.* (b) *Comparison of the two groups that were separated on the basis of lactate extraction ratios (same symbols as Fig. 1). Before propranolol pyruvate extraction was significantly lower at all but the first pacing rate in the five patients with abnormal lactate extraction* (△) *than in the other patients* (▽).
(c) *Comparison of the two groups after propranolol. The differences between the groups were no longer significant (*p < 0·05).*

butyrate, acetoacetate, free fatty acids, and glycerol did not change with heart rate, so the results at each pacing rate are not considered separately.

Arterial concentration of hydroxybutyrate fell from 0·180 ±0·018 mmol/l to 0·155 ±0·013 mmol/l after propranolol ($p < 0{\cdot}05$), but the small decrease in extraction from 0·058 ±0·008 mmol/l to 0·051 ± 0·008 mmol/l was not significant. Extraction was closely related to arterial concentration before and after the drug ($r = 0{\cdot}87$, $p < 0{\cdot}001$; $r = 0{\cdot}86$, $p < 0{\cdot}001$).

Arterial concentration of acetoacetate (0·101 ± 0·013 mmol/l and 0·113 ±0·01 mmol/l) and extraction (0·047 ±0·005 mmol/l and 0·050 ±0·005 mmol/l) were similar before and after propranolol, and extraction was related to arterial concentration ($r = 0{\cdot}93$, $p < 0{\cdot}001$; $r = 0{\cdot}96$, $p < 0{\cdot}001$).

Free fatty acid concentrations were measured in 11 patients. Arterial concentration decreased from 0·739 ±0·039 mmol/l to 0·584 ±0·028 mmol/l ($p < 0{\cdot}01$) after propranolol, but the fall in extraction from 0·131 ±0·015 to 0·125 ±0·017 mmol/l was not significant. Extraction was related to arterial concentration only before the drug ($r = 0{\cdot}49$, $p < 0{\cdot}01$).

Glycerol concentrations were measured in nine patients. After propranolol arterial concentration fell from 0·058 ±0·003 to 0·047 ±0·003 mmol/l ($p < 0{\cdot}01$), but extraction did not change. Glycerol release was common and extraction was not related to arterial concentration.

Arterial concentration and extraction of free fatty acids, ketone bodies, and glycerol did not differ significantly between the patients who did or who did not develop abnormal lactate extraction.

Oxygen extraction ratios were calculated for the 11 patients in whom fatty acids were measured (Table 2).

HAEMODYNAMIC RESULTS

Basal heart rate differed between individuals, so the pacing rates used were not identical in all patients (Fig. 3). The pacing rates before and after propranolol were in close agreement (82 ±4, 109 ±3, 132 ±4, and 147 ±4 bpm before, and 81 ±4, 109 ±3, 131 ±4, and 147 ±4 bpm after the drug). Cardiac output was lower after propranolol at all heart rates, significantly so at the second, third, and fourth pacing rates. Left ventricular body systolic pressure tended to fall as heart rate increased, and after propranolol was significantly lower at the third and fourth pacing rates. Left ventricular end-diastolic pressure rose from 11 ±1 mmHg at the lowest pacing rate to 19 ±2 mmHg at the highest pacing rate ($p < 0{\cdot}01$). After propranolol it was significantly lower at the second (8 ±1 mmHg compared with 11 ±1 mmHg: $p < 0{\cdot}05$) and fourth pacing rates (14 ±3 compared with 19 ±1 mmHg). The maximum rate of rise of left ventricular pressure decreased significantly after propranolol at the second, third, and fourth pacing rates and KV_{max} was significantly lower after the drug at the first three pacing rates.

Before propranolol coronary sinus blood flow

Table 2 *Oxygen extraction ratios at lowest pacing rate*

	Before propranolol	*After propranolol*
Lactate	14·6% ±2·9	16·5% ±3·1
Pyruvate	1·0% ±0·4	0·8% ±0·2
Hydroxybutyrate	7·8% ±1·6	8·1% ±1·2
Acetoacetate	5·2% ±1·2	7·3% ±1·2
Free fatty acids	86·9% ±14·6	91·7% ±9·7
Total	115·4% ±15	124·9% ±11·7

Pre- and postpropranolol values do not differ significantly.

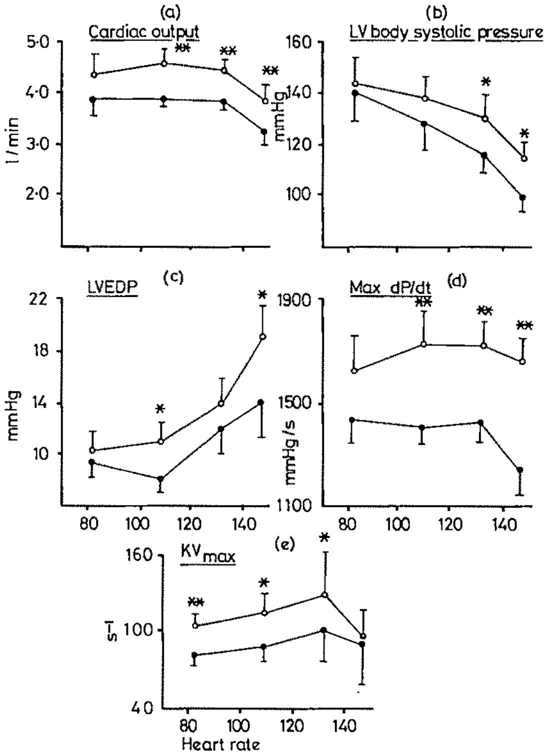

Fig. 3 *Haemodynamic results. Mean ± SEM of all patients at each pacing rate. Open circles, before propranolol; closed circles, after propranolol.* *$p < 0{\cdot}05$ **$p < 0{\cdot}01$ *when pre- and postpropranolol values are compared.*

(Fig. 4) increased as heart rate was raised, from 216±38 ml/min (range 99 to 604 ml/min) at the lowest pacing rate, to 374±74 ml/min (range 180 to 940 ml/min) at the highest pacing rate. The response of coronary sinus flow to pacing varied between patients. In nine, it rose progressively with each increment in heart rate, in two there were only small increases in flow between the lowest and highest pacing rates (case 12: 443 to 470 ml/min; case 13: 187 to 220 ml/min). In two patients, flow increased with the initial increments in heart rate and then reached a plateau (case 9: 104, 185, 202, and 202 ml/min; case 10: 604, 940, 940, and 940 ml/min). After propranolol, coronary sinus flow in the group as a whole was significantly lower only at the highest pacing rate: 329±62 ml compared with 374±74 ml/min (p<0·02).

Arterial-coronary sinus oxygen difference did not change with heart rate or propranolol administration, so coronary sinus flow and calculated myocardial oxygen consumption were closely related. At the lowest pacing rate myocardial oxygen uptake was 20·4±3·8 ml/min, range 10·1 to 57·7 ml/min. After propranolol it was significantly lower only at the third and fourth pacing rates; 25·4±6 compared with 30·8±7·5 ml/min (p<0·005) and 32·6±7·3 compared with 37·1±7·1 ml/min (p<0·01).

In this group of patients oxygen uptake bore no relation to the product of either left ventricular body systolic pressure and heart rate or systolic pressure time index and heart rate, and was not related to left ventricular minute work (Fig. 5). Calculated myocardial efficiency (Table 1) showed

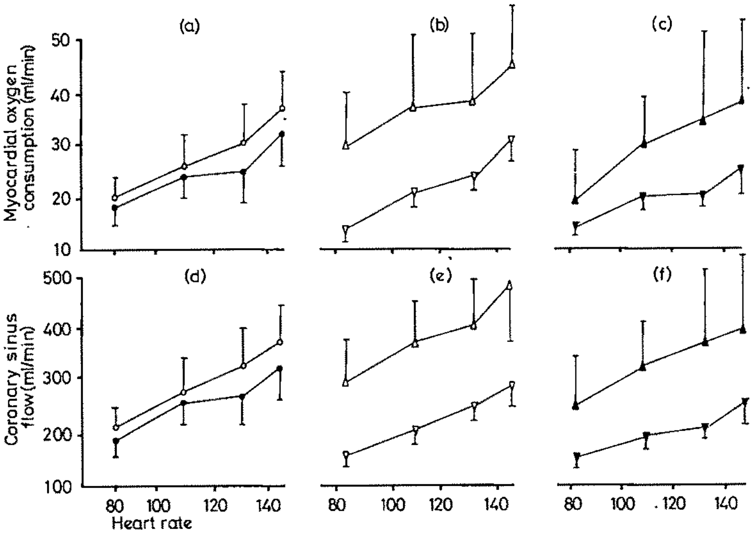

Fig. 4 Upper panels: *Myocardial oxygen consumption mean ±SEM of* (a) *all patients at each heart rate. Open circles, before propranolol; closed circles, after propranolol.* (b) *Before propranolol. Comparison of the five patients who developed ischaemia* (△) *with the other eight patients*(▽). (c) *After propranolol. Comparison of the two groups.*
Lower panels: *Coronary sinus blood flow* (d) *mean ±SEM of all patients;* (e) *before propranolol: comparison of the two groups;* (f) *after propranolol. Comparison of the two groups.*

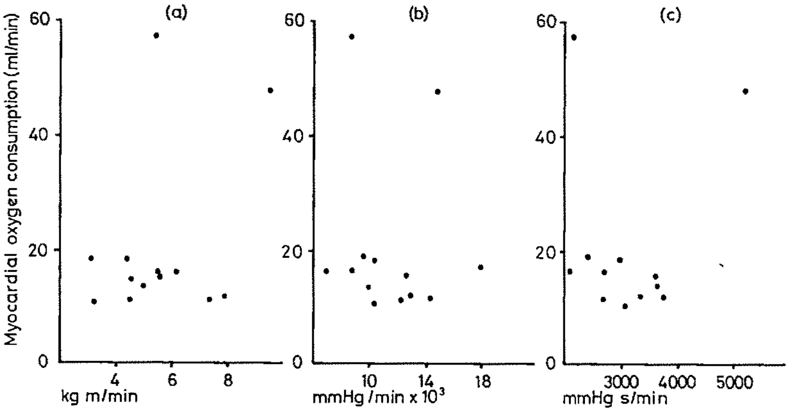

Fig. 5 *Myocardial oxygen consumption at the lowest pacing rate before propranolol plotted against* (a) *left ventricular minute work,* (b) *the product of peak left ventricular body pressure and heart rate,* (c) *the product of systolic pressure time index and heart rate. For the group as a whole myocardial oxygen consumption was not related to any of these indices of left ventricular work.*

a wide range of values at the lowest pacing rate, was normal in only two patients (cases 4 and 9), and did not change after propranolol.

RELATION BETWEEN METABOLIC AND HAEMODYNAMIC RESULTS

The five patients who developed abnormal lactate metabolism on pacing did not differ significantly from the other eight patients in age, severity of obstruction, cardiac output, left ventricular end-diastolic pressure, KV_{max}, or max dP/dt. The changes in these indices induced by pacing were similar in the two groups. Inspection of the left ventricular cineangiograms, however, suggested that the five patients with abnormal lactate metabolism at high heart rates had more severe and extensive hypertrophy (generalised hypertrophy in addition to septal thickening in four, and gross septal hypertrophy in the fifth). At the lowest pacing rate their mean myocardial oxygen uptake was $30{\cdot}8 \pm 9{\cdot}2$ compared with $14{\cdot}2 \pm 1{\cdot}0$ ml/min ($p < 0{\cdot}05$). Left ventricular minute work did not differ, so calculated myocardial efficiency tended to be lower in these five patients. On pacing, all eight patients with normal lactate extraction showed progressive increases in coronary sinus flow with each increment in heart rate. Of the five patients who became ischaemic, this pattern was seen in only one (case 11), while in two there was little increase in flow between lowest and highest pacing rates (cases 12 and 13), and in two others, flow reached a plateau (cases 9 and 10).

In the five "ischaemic" patients, at the highest pacing rate propranolol reduced cardiac output, left ventricular body systolic pressure, and hence left ventricular minute work (Table 3). Myocardial oxygen consumption showed little change in two (cases 11 and 13) but fell in the other three patients by 15 per cent (case 10), 25 per cent (case 9), and 30 per cent (case 12). There was a major increase in myocardial lactate extraction after propranolol in only one—the patient (case 12) who sustained the largest fall in oxygen consumption.

Discussion

The normal myocardium derives the majority of its energy supply from the oxidation of free fatty acids, glucose, and lactate, with small contributions from the oxidation of ketone bodies and pyruvate.[23] These substrates are extracted by the heart from arterial blood in proportion to their concentrations. In our patients, at the lowest pacing rate myocardial substrate extraction was broadly similar to results reported in normal subjects[24–26] and the total of the oxygen extraction ratios exceeded 100 per cent; thus myocardial oxygen consumption could be accounted for by the complete oxidation of the substrates extracted. That the total exceeded 100 per cent may have been a result of inaccuracy in calculated free fatty acid oxygen extraction ratio, as complete oxidation is not the invariable fate of extracted free fatty acids.[27]

Lactate by oxidation and glucose by glycolysis are both converted to pyruvate, which the heart can also extract from arterial blood. If pyruvate cannot be oxidised it is converted to lactate, and the production of lactate and its release into coronary venous blood are characteristic findings in ischaemia.[28] At the lowest pacing rate all our patients had high lactate and pyruvate extraction ratios. As heart rate increased extraction ratios remained high in eight patients, but in five fell progressively to levels comparable to those observed during pacing-induced angina in patients with coronary artery disease studied in the laboratory.[12] In normal subjects myocardial extraction of carbohydrates is related inversely to free fatty acid concentration[29] and ketone body extraction.[25] For this reason it is difficult to define a lower limit of lactate extraction below which ischaemia can be diagnosed confidently, and considered in isolation the extraction ratios measured at the middle pacing rates in the five patients who subsequently became ischaemic were not definitely abnormal. However, this decline could not be explained by changes

Table 3 *Effects of propranolol at highest pacing rate upon five patients with low or negative lactate extraction ratios*

Case no.	*LVMW (kg m/min)*		*MVO$_2$ (ml/min)*		*Efficiency (%)*		*CSF (ml/min)*		*CO (l/min)*		*CSF/CO%*		*Lactate extraction ratio (%)*	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
9	3·6	2·3	22·0	16·4	9·7	7·8	202	174	3·15	2·98	6·4	5·8	–10·5	–34·6
10	4·99	3·49	92·4	77·8	3·3	2·7	948	780	4·99	3·49	19·0	22·4	–18·7	4·3
11	2·38	2·30	43·6	44·1	3·3	3·1	532	519	2·83	2·72	18·8	19·1	2·5	6·6
12	7·95	4·67	47·0	33·0	10·2	8·5	470	331	3·96	3·83	11·9	8·6	2·7	43·8
13	4·7	3·6	22·0	20·0	13·0	10·7	229	229	4·1	2·8	5·9	8·1	–33·4	–46·4

LVMW, left ventricular minute work; MVO$_2$, myocardial oxygen consumption; CSF, coronary sinus blood flow; CO, cardiac output.

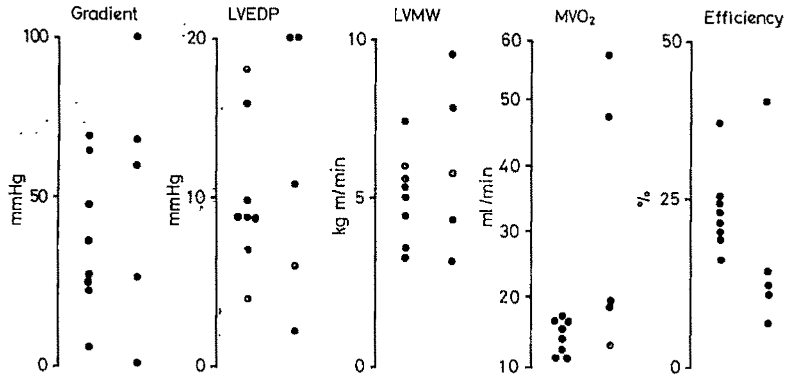

Fig. 6 *Resting gradient, left ventricular end-diastolic pressure, left ventricular minute work, myocardial oxygen consumption, and estimated efficiency at the lowest pacing rate in the eight patients with normal lactate extraction* (on the left) *and the five patients who became ischaemic on pacing* (on the right).

in free fatty acid or ketone body extractions. Thus we identified a group of patients with HOCM and angiographically normal coronary arteries in whom pacing provoked a progressive decline in aerobic carbohydrate metabolism and frank ischaemia at the highest pacing rate, suggesting that myocardial oxygen demand began to exceed supply even after a small increase in heart rate.

Four patients who had a history of angina of effort had normal myocardial lactate extraction on pacing. In patients with coronary artery disease pacing is less effective than exercise as a means of provoking evidence of ischaemia.[30] This may be particularly true in HOCM, as exercise may increase outflow obstruction,[3] and hence ventricular systolic pressure, whereas in this study ventricular pressure tended to fall as pacing rate increased.

Although we were able to separate our patients into two groups on the basis of pacing-induced changes in lactate and pyruvate extraction, this does not imply the existence of two distinct varieties of HOCM. There were no consistent haemodynamic differences between the two groups. The abnormal geometry and regional variation of wall thickness preclude the estimation of left ventricular mass, so a formal comparison of severity of hypertrophy could not be made. In only one of the patients with abnormal lactate extraction, however, was hypertrophy confined to the interventricular septum, and none of the patients with normal lactate metabolism had the massive hypertrophy seen in cases 10 and 12.

Before discussing coronary sinus blood flow and myocardial oxygen consumption, the method of their estimation should be considered. Coronary sinus flow approximates to the blood supply of the left ventricle,[31] though this has not been substantiated in HOCM. If the Ganz catheter is sited too proximally in the coronary sinus, then flow is overestimated because of reflux of atrial blood; this error can be excluded by injecting cold saline into the right atrium.[14] Flow is underestimated by about 30 per cent if the catheter is advanced beyond the entry of the posterior interventricular vein.[17] The accuracy of constant infusion thermodilution has been established for flows up to 500 ml/min[17];

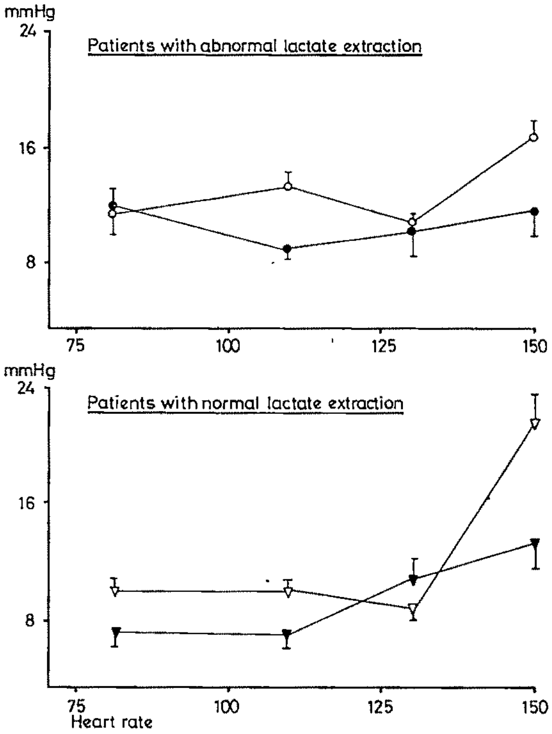

Fig. 7 *Left ventricular end-diastolic pressure at each pacing rate in the ischaemic and non-ischaemic patients. Open symbols, before propranolol; closed symbols, after propranolol.*

one of our patients had flows in excess of this value. Under these circumstances small changes in temperature have a large effect upon calculated flow, so the absolute values of flow and hence myocardial oxygen consumption are liable to be inaccurate. Despite these limitations it is unlikely that the large differences observed between patients were solely the result of methodological error.

When the results for all 13 patients were considered together, myocardial oxygen consumption could not be related to gradient, or to any index of ventricular work. As oxygen consumption was not normalised for ventricular mass, the range of values may reflect large differences in severity of hypertrophy, as in other causes of hypertrophy oxygen consumption is related to ventricular mass.[32] If this were the explanation then it would follow that hypertrophy was not related to work or obstruction, and this lack of correlation is well documented in HOCM.[3 4]

The disparity between external work and myocardial oxygen consumption can be examined by estimating myocardial efficiency.[22] Only two of the patients studied had normal efficiency (approximately 40%), and it is of interest that in both cases hypertrophy was limited to the septum. Low efficiency in the other patients was not a result of dissipation of energy by outflow obstruction, as left ventricular body systolic pressure was used to calculate minute work, but might have been the result either of reduced efficiency in the production of energy from the oxygen consumed, or in the conversion of this energy into measurable external work. The former possibility is unlikely, as oxidation of the substrates extracted would account for measured oxygen consumption. The oxygen cost of external work is increased by ventricular dilatation,[33] but, as is usual in HOCM, our patients had small or normal sized ventricular cavities. Recent studies upon the shape of the septum[34] and fibre disarray in HOCM[35 36] have suggested that areas of the myocardium may contract isometrically during systole, and as a consequence of the shape of the septum isometric contraction would not increase intraventricular pressure. Under these circumstances the oxygen consumed by some areas of the myocardium would not produce measurable external work, resulting in low myocardial efficiency.

The patients with the four highest values of myocardial oxygen consumption had the four lowest values of efficiency, and all developed ischaemia on pacing. The other patient who became ischaemic had relatively low myocardial oxygen consumption and normal efficiency, but as the heart rate increased, coronary sinus flow reached a plateau, failing to rise with the final increment in heart rate. Of the five patients who became ischaemic on pacing, only one showed progressive rises in coronary sinus flow with each increment in heart rate, whereas this pattern was seen in each of the other eight. In severe hypertrophy caused by tight aortic stenosis there is evidence to suggest that the coronary vasculature is near maximal dilatation at rest.[5] Aortic diastolic pressure was not measured in all patients at all pacing rates, so coronary vascular resistance has not been calculated, but in the two patients whose coronary sinus flow barely changed with pacing (cases 12 and 13) aortic pressure did not fall as heart rate increased, implying that the coronary vasculature failed to dilate sufficiently in response to pacing.

No single factor predicted which patients became ischaemic on pacing, but each of the five that did had at least one of the following features, none of which was seen in the other eight patients: high myocardial oxygen consumption ($>18{\cdot}7$ ml/min) and low efficiency ($<15\%$) at the lowest pacing rate, or a failure of coronary sinus flow to increase with each increment in heart rate.

The beneficial effect of beta-blocking drugs upon angina may result from reduction of myocardial oxygen demand secondary to their haemodynamic actions.[37–39] When heart rate is controlled by pacing, beta-blockade has little effect upon myocardial oxygen consumption,[11 40] but may still improve lactate extraction or anginal threshold[10 11] in patients with coronary artery disease, suggesting that it modifies the metabolism of ischaemic myocardium independently of haemodynamic effects. This might be a result in part of reduction of arterial free fatty acid concentration.[12]

In this study propranolol did not change myocardial lactate extraction. Its lack of effect upon the non-ischaemic patients was not surprising, as their consistently high lactate and pyruvate extraction ratios suggest that aerobic carbohydrate metabolism before the drug was not limited by lack of oxygen or high rates of free fatty acid catabolism. In two ischaemic patients (cases 11 and 13) propranolol had little effect upon oxygen consumption, coronary sinus flow, or lactate extraction. Thus in these patients there was no evidence that propranolol had a direct effect upon the metabolism of ischaemic myocardium. Reduction of 15 and 25 per cent in myocardial oxygen uptake after propranolol (cases 9 and 10) was not accompanied by a major change in lactate extraction; the decrease in oxygen demand was balanced by a commensurate decrease in supply. If the coronary vasculature were maximally dilated, and the length of diastole fixed by pacing, then after propranolol coronary flow would fall in proportion to cardiac output. In these two patients coronary sinus flow expressed as a percentage of cardiac output was similar before and after the drug. While the reduction of myocardial oxygen consumption by propranolol was probably a result of decreased pressure-work and contractility, the accompanying fall in cardiac output may have been the reason for the failure of decreased oxygen demand to abolish ischaemia. The only patient in whom propranolol had a distinct beneficial effect upon lactate extraction (case 12) sustained a large fall in myocardial oxygen consumption but only a minor reduction in cardiac output after the drug.

Pacing of the normal heart reduces left ventricular end-diastolic pressure[41 42] whereas in our patients it rose between the lowest and highest pacing rates. In patients with coronary artery disease pacing-induced ischaemia may be associated with an increase in end-diastolic pressure,[43] but in this study pressure rose both in ischaemic and non-ischaemic patients. After propranolol, end-diastolic pressure was lower at the highest pacing rate, and this reduction could not be explained by relief of ischaemia. Propranolol increases diastolic ventricular compliance in HOCM,[9] and the fall in end-diastolic pressure reported here may have been a result of this effect. The mechanism by which propranolol improves compliance in HOCM is not known; our results suggest that it is not related to relief of ischaemia.

We conclude that ischaemia in HOCM is a consequence either of high myocardial oxygen demand, which is excessive for the external work performed, or the inability of coronary flow to increase appropriately with heart rate. When heart rate is controlled by pacing propranolol does not influence either of these problems; nor does it appear to have a direct beneficial effect upon myocardial metabolism. These results emphasise, however, the possible deleterious effects of tachycardia in HOCM, and stress the value of using beta-blockade to reduce heart rate and prevent tachyarrhythmias.

References

1 Goodwin JF, Hollman A, Cleland WP, Teare D. Obstructive cardiomyopathy simulating aortic stenosis. *Br Heart J* 1960; **22:** 403–14.

2 Braunwald E, Morrow AG, Cornell WP, Aygen MM, Hilbish TF. Idiopathic hypertrophic subaortic stenosis: clinical, hemodynamic and angiographic manifestations. *Am J Med* 1960; **29:** 924–45.

3 Braunwald E, Lambrew CT, Rockoff SD, Ross J, Morrow AC. Idiopathic hypertrophic subaortic stenosis: 1. A description of the disease based upon an analysis of 64 patients. *Circulation* 1964; **30/31,** suppl IV: 3–119.

4 Goodwin JF, Oakley CM. The cardiomyopathies. *Br Heart J* 1972; **34:** 545–52.

5 Fallen EL, Elliot WC, Gorlin R. Mechanisms of angina in aortic stenosis. *Circulation* 1967; **36:** 480–8.

6 Cohen LS, Braunwald E. Amelioration of angina pectoris in idiopathic hypertrophic subaortic stenosis with beta-adrenergic blockade. *Circulation* 1967; **35:** 847–51.

7 Sloman G. Propranolol in management of muscular subaortic stenosis. *Br Heart J* 1967; **29:** 783–7.

8 Flamm MD, Harrison DC, Hancock EW. Muscular subaortic stenosis. Prevention of outflow obstruction with propranolol. *Circulation* 1968; **38:** 846–58.

9 Swanton RH, Brooksby IAB, Jenkins BS, Webb-Peploe MM. Haemodynamic studies of beta blockade in patients with hypertrophic obstructive cardiomyopathy. *Eur J Cardiol* 1977; **5/4:** 327–41.

10 Jackson G, Atkinson L, Oram S. Improvement of myocardial metabolism in coronary artery disease by beta-blockade. *Br Heart J* 1977; **39:** 829–33.

11 Armstrong PW, Chiong MA, Parker JO. Effects of propranolol on the hemodynamic, coronary sinus blood flow and myocardial metabolic response to atrial pacing. *Am J Cardiol* 1977; **40:** 83–9.

12 Thompson DS, Naqvi N, Juul SM, Coltart DJ, Jenkins BS, Webb-Peploe MM. Haemodynamic and metabolic effects of atenolol in patients with angina pectoris. *Br Heart J* 1980; **43:** 668–79.

13 Brooksby IAB, Swanton RH, Jenkins BS, Webb-Peploe MM. Long sheath technique for introduction of catheter tip micromanometer or endomyocardial bioptome into left or right heart. *Br Heart J* 1974; **36:** 908–12.

14 Mathey DG, Chatterjee K, Tyberg JV, Lekven J, Brundage B, Parmley WW. Coronary sinus reflux: a source of error in the measurement of thermodilution coronary sinus flow. *Circulation* 1978; **57:** 778–86.

15 Redwood DR, Scherer JL, Epstein SE. Biventricular cineangiography in the evaluation of patients with asymmetric septal hypertrophy. *Circulation* 1974; **49:** 1116–21.

16 Kolettis M, Jenkins BS, Webb-Peploe MM. Assessment of left ventricular function by indices derived from aortic flow velocity. *Br Heart J* 1976; **38:** 18–31.

17 Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow in man by constant thermodilution in man. *Circulation* 1971; **44:** 181–95.

18 Hohorst HJ, Kreutz FH, Bücher T. Über Metabolitgehalte und Metabolit-konzentrationen in der Leber der Ratte. *Biochemische Zeitschrift* 1959; **332:** 18–46.

19 Williamson DH, Mellanby J, Krebs HA. Enzymatic determination of D(—) B-Hydroxybutyric acid and acetoacetic acid in blood. *Biochem J* 1962; **82:** 90–6.

20 Kreutz FH. Enzymatische Glycerinbestimmung. *Klin Wochenschr* 1962; **40:** 362–3.

21 Carruthers M, Young DAB. Free fatty acid estimation by a semi-automated fluorimetric method. *Clin Chim Acta* 1973; **49**: 341–8.

22 Bing RJ, Michal G. Myocardial efficiency. *Ann NY Acad Sci* 1959; **72**: 555–8.

23 Bing R. Cardiac metabolism. *Physiol Rev* 1965; **45**: 171–213.

24 Bing RJ, Siegel A, Vitale A, *et al.* Metabolic studies on the human heart in vivo. I. Studies in carbohydrate metabolism of the human heart. *Am J Med* 1953; **15**: 284–96.

25 Bing RJ, Siegel A, Ungar I, Gilbert M. Metabolism of the human heart. II. Studies on fat, ketone and amino acid metabolism. *Am J Med* 1954; **16**: 504–15.

26 Goodale WT, Olson RE, Hackel DB. The effects of fasting and diabetes mellitus on myocardial metabolism in man. *Am J Med* 1959; **27**: 212–20.

27 Zierler KL. Fatty acids as substrates for heart and skeletal muscle. *Circ Res* 1976; **38**: 459–63.

28 Gorlin R. Evaluation of myocardial metabolism in ischemic heart disease. *Circulation* 1969; **39–40**, suppl IV: 155–63.

29 Lassers BW, Wahlqvist ML, Kaijser L, Carlson LA. Relationship in man between plasma free fatty acids and myocardial metabolism of carbohydrate substrates. *Lancet* 1971; **ii**: 448–50.

30 O'Brien KP, Higgs LM, Glancy DL, Epstein SE. Hemodynamic accompaniments of angina. A comparison during angina induced by exercise and by atrial pacing. *Circulation* 1969; **39**: 735–43.

31 Hood WB Jr. Regional venous drainage of the human heart *Br Heart J* 1968; **30**: 105–9.

32 Dodge HT, Baxley WA. Hemodynamic aspects of heart failure. *Am J Cardiol* 1968; **22**: 24–34.

33 Rodbard S, Williams CB, Rodbard D, Berglund E. Myocardial tension and oxygen uptake. *Circ Res* 1964; **14**: 139–49.

34 Hutchins GM, Bulkley BH. Catenoid shape of the interventricular septum: possible cause of idiopathic hypertrophic subaortic stenosis. *Circulation* 1978; **58**: 392–7.

35 Bulkey BH, Weisfeldt ML, Hutchins GM. Isometric cardiac contraction. A possible cause of the disorganized myocardial pattern of idiopathic hypertrophic subaortic stenosis. *N Engl J Med* 1977; **296**: 135–9.

36 Wigle ED, Silver MD. Myocardial fibre disarray and ventricular septal hypertrophy in asymmetrical hypertrophy of the heart. *Circulation* 1978; **58**: 398–402.

37 Wolfson S, Heinle RA, Herman MV, Kemp HG, Sullivan JM, Gorlin R. Propranolol and angina pectoris. *Am J Cardiol* 1966; **18**: 345–53.

38 Robinson BF. The mode of action of beta-antagonists in angina pectoris. *Postgrad Med J* 1971; **47**, suppl: 41–3.

39 Schang SJ, Pepine CJ. Effects of propranolol on coronary hemodynamic and metabolic responses to tachycardia stress in patients with and without coronary disease. *Cathet Cardiovasc Diagn* 1977; **3**: 47–57.

40 Simonsen S. Effects of atenolol (ICI 66 082) on coronary haemodynamics in man. *Br Heart J* 1977; **39**: 1210–6.

41 Linhart JW. Pacing-induced changes in stroke volume in the evaluation of myocardial function. *Circulation* 1971; **43**: 253–61.

42 Parker JO, Khaja F, Case RB. Analysis of left ventricular function by atrial pacing. *Circulation* 1971; **43**: 241–52.

43 Linhart JW, Hildner FJ, Barold SS, Lister JW, Samet P. Left heart hemodynamics during angina pectoris induced by atrial pacing. *Circulation* 1969; **40**: 483–92.

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Antibiotic prophylaxis against infective endocarditis after normal delivery—is it necessary?

D SUGRUE,* S BLAKE, P TROY, D MACDONALD

From The National Maternity Hospital, Holles Street, Dublin, Eire

SUMMARY During the years 1959 to 1978 inclusive 2165 women with rheumatic or congenital heart disease had vaginal deliveries at three large Dublin maternity hospitals. There were two (0·09%) cases of puerperal infective endocarditis, neither of which was unequivocally related to preceding childbirth during this period. Routine peripartum antibiotic prophylaxis was not given to either.

A questionnaire of the practice of 19 obstetricians in Ireland showed that 12 (63%) gave antibiotics routinely during labour and after delivery in cardiac patients, five (26%) did not, and two (11%) used them occasionally.

Peripheral vein blood was drawn serially from 0 to 30 minutes after vaginal delivery to determine the incidence of asymptomatic puerperal bacteraemia. A total of 299 cultures was obtained from 83 normal women and single blood cultures were positive in three women (3·6% of patients, 1·0% of cultures).

A review of the published reports showed that well-documented cases of infective endocarditis and of asymptomatic puerperal bacteraemia after normal vaginal delivery are uncommon. There is evidence that antibiotic prophylaxis may increase the risk of developing antibiotic-resistant endocarditis. Recommended prophylactic regimens carry a considerable risk of drug toxicity. These facts, coupled with a lack of direct evidence in support of the efficacy of antibiotic prophylaxis, suggest that routine peripartum antibiotic prophylaxis is not indicated.

The occurrence of infective endocarditis after abortion,[1–3] the insertion of intrauterine contraceptive devices,[4 5] and vaginal delivery[6–10] is used as support for routine antibiotic prophylaxis during normal labour and childbirth in patients with known heart disease. Published work provides little evidence for the need, and none for the efficacy of antibiotics in preventing endocarditis.

Prophylactic antibiotics have not been given routinely at delivery of cardiac patients at the National Maternity, Coombe Lying-In, and Rotunda Maternity Hospitals, Dublin, during the years 1959 to 1978. This report consists of three parts:

(a) A survey by questionnaire in which obstetricians working in Ireland were asked about their practice in this regard.
(b) An investigation of the incidence of asymptomatic bacteraemia after vaginal delivery in a group of normal women.
(c) A brief review of cases of infective endocarditis which occurred after delivery without antibiotic prophylaxis.

Subjects and methods

Details of pregnancies complicated by heart disease and cases of postpartum endocarditis were obtained from the Dublin Maternity Hospitals Annual Reports 1959 to 1978.[11]

A questionnaire containing the following three questions was sent to 19 obstetricians in Ireland:

(a) Do you routinely prescribe antibiotics during labour and the puerperium in cardiac patients?
(b) If yes, please give details.
(c) Has there been a case of infective endocarditis after delivery at your unit during the past five years?

Fifty non-cardiac patients had four blood cultures each, taken immediately after placental separation and five, 10, and 30 minutes later. Thirty-three patients had three cultures each,

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one taken at placental separation and two within the following 10 minutes. Patients with prolonged rupture of membranes, those with overt infection, or those already taking antibiotics were excluded from the study. Five patients had forceps delivery, four had manual removal of the placenta, and the remainder had uncomplicated vaginal deliveries. Antecubital venepuncture was performed under aseptic conditions; 5 ml blood were placed in culture bottles containing fluid thioglycollate medium. Bottles were incubated at 37°C and subcultures onto blood agar plates, incubated aerobically and anaerobically, were made within 24 hours and again at 48 hours, 72 hours, and 10 days. Growths were Gram-stained and identified.

Results

At the National Maternity, Coombe Lying-In, and Rotunda Hospitals, Dublin, during the years 1959 to 1978 inclusive, 2165 women with rheumatic or congenital heart disease had vaginal deliveries. Nineteen obstetricians (100%) replied to the questionnaire. Twelve (63%) gave antibiotics routinely, five (26%) did not, and two (11%) used them occasionally, for example for instrumental delivery. Among those who used antibiotics routinely, nine gave oral ampicillin during labour and for five days post partum; three did not state their choice of antibiotic. Only two respondents gave details of dosage; both used ampicillin 250 mg four times daily.

Three blood cultures were positive from a total of 299 obtained from 83 patients, giving a positive isolation rate of 3·61 per cent for patients and 0·1 per cent for cultures. The three positive cultures were all from different patients. One grew anaerobic Gram-negative bacilli and two a mixed growth. One of the positive cultures was obtained from a patient who had a manual removal; the other two were obtained after uncomplicated vaginal deliveries. All were considered to be of doubtful significance.

Table 1 *Clinical details of two cases of infective endocarditis which occurred after vaginal delivery without antibiotic prophylaxis*

Case no.	*Age at diagnosis (y)*	*Interval between delivery and diagnosis (h)*	*Heart lesion and NYHA grade*[12]	*Blood culture*	*Maternal outcome*
1	33	12	+MS MR grade IV	Negative	Recovery
2	29	48	MS MR grade IV	Negative	Recovery

+MS, mitral stenosis; MR, mitral regurgitation.‡NYHA, New York Heart Association.

Two cases of endocarditis had been recorded after vaginal delivery (Table 1). Neither had had antibiotic prophylaxis. The diagnosis was based on clinical features without confirmation by positive blood cultures and in each case a manual removal had been performed. An additional case of possible puerperal endocarditis in which prophylactic antibiotics had been used was reported in the survey by questionnaire.

Discussion

The results of the survey by questionnaire confirm the divergence of opinion on the need for routine antibiotic prophylaxis after normal vaginal delivery.

The low rate of isolation of bacteria in the present study highlights the infrequency of asymptomatic puerperal bacteraemia. Even though the possible transience of bacteraemic peaks and subliminal concentrations of bacteria in blood may lead to underestimation of its true incidence,[13] substantial bacteraemia was not seen to occur in any patient.

Table 2 compares the incidence of puerperal bacteraemia in the present study with the incidence in four published series.[14–17] Thirty-six patients from a combined total of 1116 had positive cultures (3·23%). Twelve of these patients, however, had concurrent symptomatic infections giving a true incidence of asymptomatic puerperal bacteraemia after vaginal delivery of 2·15 per cent. In contrast to this, peripheral blood bacterial isolation rates after dental extraction have varied from 60 per cent[18] to 90 per cent[13] and after genitourinary tract manipulation from 7·3 per cent[19] to 85·9 per cent.[20] Isolation rates of this magnitude place cardiac patients at considerable risk of contracting endocarditis and fully justify routine antibiotic prophylaxis. The argument of high risk based on bacterial isolation rates cannot be used to justify routine prophylaxis after normal delivery of cardiac patients, however. Moreover, such routine prophylaxis may be harmful. Antibiotic resistance occurs in buccal commensal flora within 48 hours of administration[21] and resistant streptococci persist in diminished numbers for several weeks,[22] thereby enhancing the risk of antibiotic-resistant endocarditis. Additional evidence to support a policy of non-administration of routine prophylactic antibiotics comes from Marquis at the Simpson Memorial Maternity Pavilion, Edinburgh.[23] In that hospital, peripartum antibiotic prophylaxis is only given when sepsis is suspected but infective endocarditis has not occurred after delivery in

Table 2 *Incidence of puerperal bacteraemia in 1121 patients: present series and review of published reports*

Authors	*Year*	*No. of patients*	*Blood cultures*			*Organisms isolated*
			Total no.	*Time*	*Per cent positive*	
Burwell and Metcalfe[14]	1948	17	74	Not stated		—
Readleaf and Fadell[15]	1959	101	202	At delivery; within 24 h	7·2	Micrococcus and haemolytic streptococcus
Baker *et al.*[16]	1966	396	1779	At delivery; 12, 24, 48 h	0·39	*Esch coli*, *Aerobacter pseudomonas*
Baker and Hubbell[17]	1967	519	2583	Delivery of placenta; 15 min, 30 min, 12 h, 24 h	0·77	*Esch coli*, *Strep. viridans*, bacteroides, pseudomonas
Present series	1979	83	299	Within 30 min of delivery	0·1	Anaerobic Gram-negative bacilli, mixed growth

over 1750 cardiac patients during a 25-year period.

Review of the published reports showed a total of 27 cases of endocarditis after uncomplicated vaginal delivery.[6–11 24] The causative role of delivery in precipitating endocarditis was equivocal in many instances. It is noteworthy that both cases of postpartum endocarditis in the present series were culture negative, and in one instance the diagnosis was made within 12 hours of delivery, thereby casting some doubt on the causative role of this. The specific hazard of enterococcal endocarditis after delivery has been cited as evidence in favour of routine peripartum antibiotic prophylaxis.[25 26] Eleven cases of pregnancy-related enterococcal endocarditis have been reported,[24 27 28] but only one was unequivocally related to normal childbirth.[24] The remaining cases followed abortion, caesarean section, or occurred during pregnancy.[27 28]

The occurrence of both cases of endocarditis and one case of asymptomatic bacteraemia after manual removal of the placenta suggests that this procedure does carry an increased risk of endocarditis. Two additional cases of endocarditis after manual removal have been reported.[9] It is prudent therefore to give antibiotic prophylaxis in this situation. The regimen recommended by the American Heart Association[29] is appropriate for this, that is penicillin G 2 000 000 units intramuscularly plus gentamicin 80 mg intramuscularly, or ampicillin 1 g intramuscularly or intravenously 30 minutes before the procedure. Vancomycin 1 g by intravenous infusion over 30 minutes plus streptomycin 1 g intramuscularly may be given to patients who are allergic to penicillin. The use of streptomycin however carries a risk of vestibular damage, a risk to which there is considerable individual variation in susceptibility and which is not entirely dose related.[30]

In the absence of any evidence in support of routine prophylaxis at normal delivery, coupled with the possible hazards of such a policy, we feel that this is not indicated in patients with heart disease.

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We thank Dr C M Oakley for helpful advice and criticism.

References

1 Dormer AE. Bacterial endocarditis. Survey of patients treated between 1945 and 1956. *Br Med J* 1958; **i:** 63–9.
2 Rabinovitich S, Evans J, Smith IM, January LE. A longterm view of bacterial endocarditis 337 cases 1924–1963. *Ann Intern Med* 1965; **63:** 185–98.
3 Ward H, Hickman RC. Bacterial endocarditis in pregnancy. *Aust NZ J Ostet Gynaecol* 1971; **11:** 189–91.
4 Cobbs CG. IUD and endocarditis (letter). *Ann Intern Med* 1973; **78:** 451.
5 de Swiet M, Ramsey ID, Rees GM. Bacterial endocarditis after insertion of intrauterine contraceptive device. *Br Med J* 1975; **iii:** 76–7.
6 Wheeler CH. In: Mendelson CL. Pregancy and subacute bacterial endocarditis. *Am J Obstet Gynecol* 1948; **56:** 645–54.
7 Haig DC, Gilchrist AR. Heart disease complicated by pregnancy. (Transactions of Edinburgh Medical Society.) *Edinburgh Med J* 1949; **56:** 55–75.
8 Vanderveer JB, and Kuo PT. Cardiac disease in pregnancy. *Am Heart J* 1950; **39:** 2–16.
9 Lein JN, Stander RW. Subacute bacterial endocarditis following obstetric and gynaecologic procedures. Report of 8 cases. *Obstet Gynecol* 1959; **13:** 568–73.
10 Szekely P, Snaith L. *Heart disease and pregnancy.* Edinburgh and London: Churchill Livingstone, 1974: 112.
11 Annual Reports of the National Maternity Hospital, Coombe Lying-In Hospital and Rotunda Hospital, Dublin, 1959–78.
12 New York Heart Association Criteria Committee. *Nomenclature and criteria for diagnosis of diseases of*

the heart and great vessels. 8th ed. Boston: Little Brown, 1979: 290.

13 Rogosa M, Hampp EG, Nevin TA, Wagner HN Jr, Driscoll EJ, Baer PN. Blood sampling and cultural studies in the detection of postoperative bacteremias. *J Am Dent Assoc* 1960; **60:** 171–80.

14 Burwell CS, Metcalfe J. *Heart disease and pregnancy physiology and management.* Boston: Little Brown, 1958: 277.

15 Redleaf PD, Fadell EJ. Bacteraemia during parturition. *JAMA* 1959; **169:** 1248–85.

16 Baker TH, Machikawa JH, Stapleton JJ. Asymptomatic puerperal bacteraemia. *Am J Obstet Gynecol* 1966; **94:** 903–5.

17 Baker TH, Hubbell R. Re-appraisal of asymptomatic puerperal bacteremia. *Am J Obstet Gynecol* 1967; **97:** 575–6.

18 Kaye D, ed. *Infective endocarditis.* Baltimore: University Park Press, 1976: 276.

19 Steyn JH, Logie NJ. Bacteraemia following prostatectomy. *Br J Urol* 1962; **34:** 459–62.

20 Barrington FJF, Wright HD. Bacteraemia following operations on the urethra. *J Pathol Bacteriol* 1930; **33:** 871–88.

21 Garrod LP, Waterworth P. The risks of dental extraction during penicillin treatment. *Br Heart J* 1962; **24:** 39–46.

22 Sprunt K, Redman W, Leidy G. Penicillin resistant alpha streptococci in pharynx of patients given oral penicillin. *Pediatrics* 1968; **42:** 957–68.

23 Marquis RM. Bacterial endocarditis following delivery in women with heart disease. In: Anguissola AB, Puddu V, eds. *Cardiologia d'oggi.* Turin: CG Edisioni Medico Scientifiche, 1975: 278.

24 Leaman WG, Wikingsson MB, Webster MB, Shaw CC. Caronamide and penicillin in subacute bacterial endocarditis due to streptococcus faecalis. *Ann Intern Med* 1949; **30:** 646–54.

25 Hook EW, Kaye D. Prophylaxis of bacterial endocarditis. *J Chronic Dis* 1962; **15:** 635–46.

26 Polk BF, Schoenbaum SC. Prophylactic antibiotics in obstetrics. *Clin Obstet Gynecol* 1979; **22:** 379–83.

27 Koenig MG, Kaye D. Enterococcal endocarditis. Report of 19 cases with longterm follow-up data. *N Engl J Med* 1961; **264:** 257–64.

28 Mandell GL, Kaye D, Levison ME, Hook EW. Enterococcal endocarditis: an analysis of 38 patients observed at the New York Hospital Cornell Medical Centre. *Arch Intern Med* 1970; **125:** 258–64.

29 Kaplan EL, Anthony BF, Bisno A, *et al.* Prevention of bacterial endocarditis (AHA Committee Report). *Circulation* 1977; **56:** 139A–43A.

30 Pražić M, Salaj B, Subotíc R. Familial sensitivity to streptomycin. *J Laryngol Otol* 1964; **78:** 1037–43.

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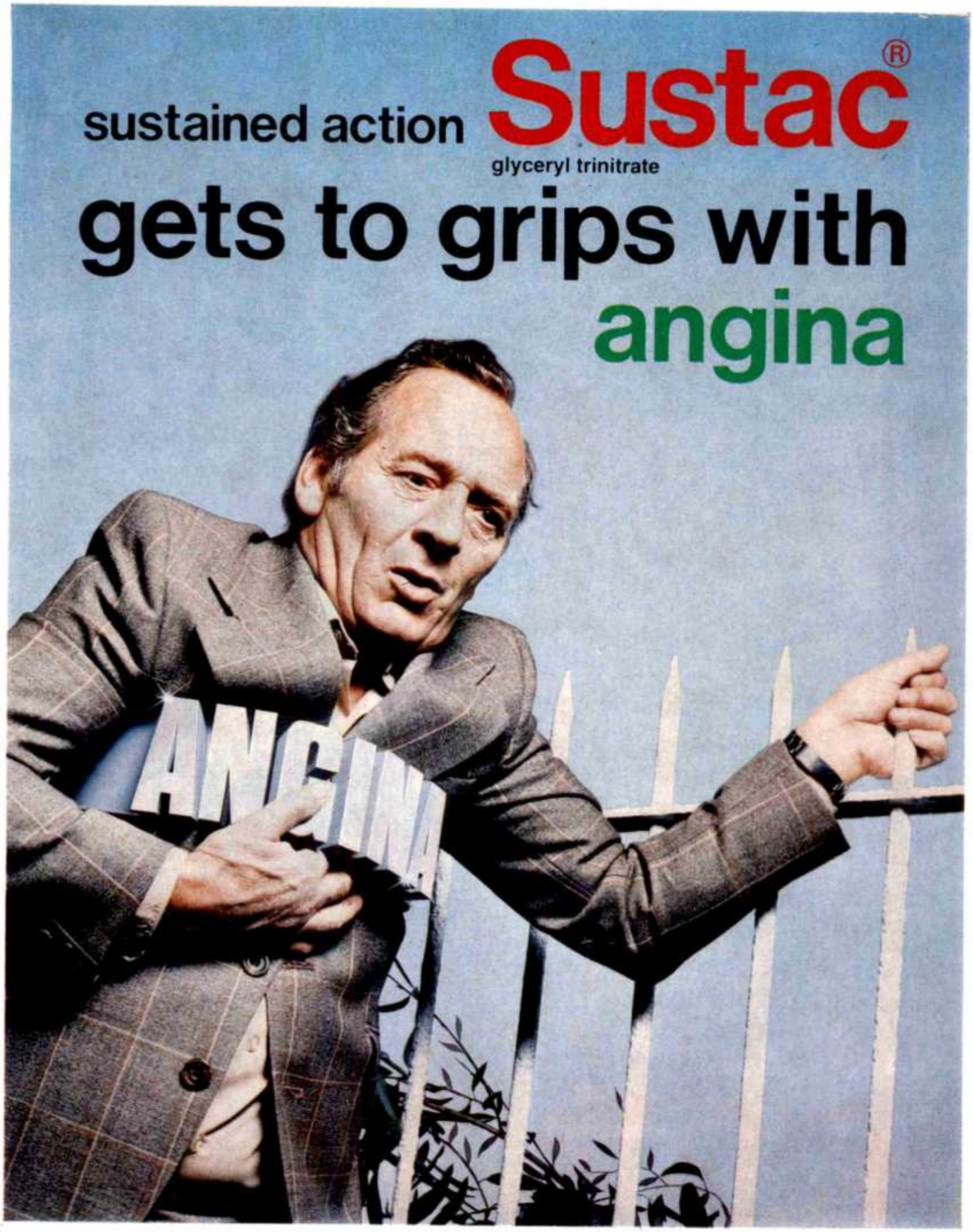

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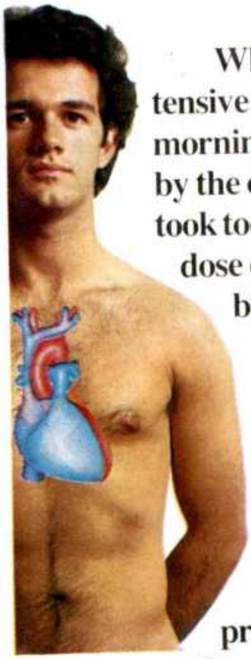

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ICI

Br Heart J 1980; **44**: 503–7

Importance of age in prehospital and hospital mortality of heart attacks

R G WILCOX, J R HAMPTON

From Department of Medicine, University of Nottingham

SUMMARY Prehospital and hospital fatality rates were calculated for each 10-year age group of 2788 patients transported to hospital with heart attacks. The prehospital fatality rate rose progressively from 4 per cent in the youngest age group to 45 per cent in the oldest. There was no age-related difference between the groups in the interval between the onset of symptoms and the first call for help, and a similar proportion of each group summoned a general practitioner. Among those admitted to hospital there was a progressive rise with age in the proportion eventually found to have had a definite or probable myocardial infarction, and among such patients the hospital fatality rate rose from 8 per cent in the youngest group to 35 per cent in the oldest. There was a progressive rise with age in the symptoms and signs of, and treatment for, heart failure.

Reported fatality rates from myocardial infarction can only be interpreted if the ages of the patients are known in detail.

The importance of taking into account a patient's age when assessing his chances of surviving a myocardial infarction was pointed out by Peel in 1955.[1] Since then age has been incorporated into several "prognostic indices"[2–5] yet papers continue to appear which claim very low hospital fatality rates for patients with myocardial infarction with little or no mention of the age of the population studied.[6 7] In this paper we re-emphasise the extreme importance of the patients' ages in any study of the outcome of myocardial infarction.

Methods

All patients who required admission for emergency medical problems in Nottingham and its surroundings are referred to the two teaching hospitals. During a four-year period between 1973 and 1977 data were collected daily by a non-medical graduate research assistant on all patients referred to these hospitals with suspected heart attacks. The patients were identified from ambulance and hospital admission records, and were followed up until they died in, or were discharged from, hospital. Coroners' records were inspected for any patient who died before admission, so that those who had had a myocardial infarction could be identified.

After a patient's death or discharge the data collected, together with copies of all electrocardiograms and the discharge summary or necropsy report, were inspected by a physician (JRH) and the patient was either excluded from the study if he or she had been found to have some disease other than a heart attack, or was placed in one of the following five diagnostic categories.

(i) *Definite myocardial infarction*—patients with a convincing history of myocardial infarction together with unequivocal electrocardiographic abnormalities (appearance of Q wave and sequential ST segment changes) and a rise in cardiac enzyme values to greater than double the normal upper limit. Patients were also included in this category if there was definite necropsy evidence of myocardial infarction.

(ii) *Probable myocardial infarction*—patients with a convincing clinical history together with either unequivocal electrocardiographic abnormalities or a rise in plasma cardiac enzyme levels to greater than twice the normal upper limit. Patients were also included in this category if there was necropsy evidence of coronary artery disease but no other cause was found for death.

(iii) *Possible myocardial infarction*—patients with a convincing history together with an abnormal electrocardiogram that was not typical of recent myocardial infarction, or a rise in serum enzyme

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Table 1 *Number of patients in each 10-year age group who were found dead on arrival in hospital*

Age group	*≤34*	*35–*	*45–*	*55–*	*65–*	*75–*	*85–*	*Total*
Number of patients	23	156	588	886	810	283	42	2788
% men	78	89	84	78	68	51	52	74
% patients at home when symptoms began	68	62	63	66	69	72	80	67
Dead on arrival at hospital (%)	1 (4%)	23 (15%)	89 (15%)	189 (21%)	261 (32%)	123 (43%)	19 (45%)	705 (25%)

levels which did not reach twice the upper limit of normal.

(iv) *Ischaemic heart disease*—patients with a clear history of previous myocardial infarction or angina, together with an abnormal electrocardiogram but nothing to suggest a recent change, and with normal serum enzyme values.

(v) *Chest pain of uncertain cause*—patients for whom no adequate diagnosis could be made.

Categories (i) and (ii) combined correspond approximately to the WHO definition of definite myocardial infarction.

The data were transferred to 80 column cards and analysed by computer.

Results

(1) PREHOSPITAL EVENTS

Studies were made on 2788 patients, and Table 1 shows the number in each 10-year age group. Of the patients aged 44 and below, 87 per cent were men, but with increasing age the proportion of women rose and in the groups aged 75 or over, and 85 or over, there were equal numbers of men and women (Table 1). Seven hundred and five (25%) patients were found to be dead on arrival at hospital, and the prehospital fatality rate increased progressively with age so that among the oldest age group 45 per cent of the patients were dead on arrival. Within each age group the prehospital fatality rate was similar for men and for women.

Table 1 shows that in all age groups except the two oldest, about two-thirds of the patients called for help from their homes. In most cases the symptoms of the heart attack began while the patient was at home, but among the younger age groups there were some patients who developed chest pain at work but delayed calling for help until they had returned home. The first call for help was made to a general practitioner by 1390 (50%) of the patients and for the remainder an emergency ambulance was summoned directly by a member of the public. There was a distinct difference in this respect between patients who were found to be dead on arrival at hospital and those who were admitted. Among those who died before admission a general practitioner was called to between 0 and 13 per cent of the different age groups, without any age-related pattern. Among those who were admitted to hospital, the initial call for help was made to a general practitioner in 62 to 67 per cent of patients. More elderly patients were found dead on arrival at hospital, so in the group as a whole emergency ambulances were summoned to a higher proportion of elderly people.

There were also distinct differences between those patients who were dead on arrival and those who were admitted to hospital in terms of the interval between the onset of symptoms and the first call for help. Among those found dead on arrival, an ambulance had been summoned within 30 minutes of the onset of symptoms for between 69 and 89 per cent of patients in the different age groups. No information could be obtained in 106 (15%) of these 705 patients, mainly because they lived alone and were found dead; there was, however, no trend to suggest that the older patients who were dead on arrival at hospital delayed longer than the younger ones before calling for help. There was a much greater interval between the onset of symptoms and

Table 2 *Duration of symptoms before the call for help among patients admitted to hospital*

Age group	*≤34*	*35–*	*45–*	*55–*	*65–*	*75–*	*85–*
Call for help (cumulative %)							
Within 30 minutes	4	25	16	16	20	16	16
Within 1½ hours	44	42	38	37	40	35	48
Within 4 hours	48	68	58	57	59	68	54
Within 10 hours	75	80	71	72	66	85	81
% calling for help after 10 hours	25	20	29	28	34	15	19

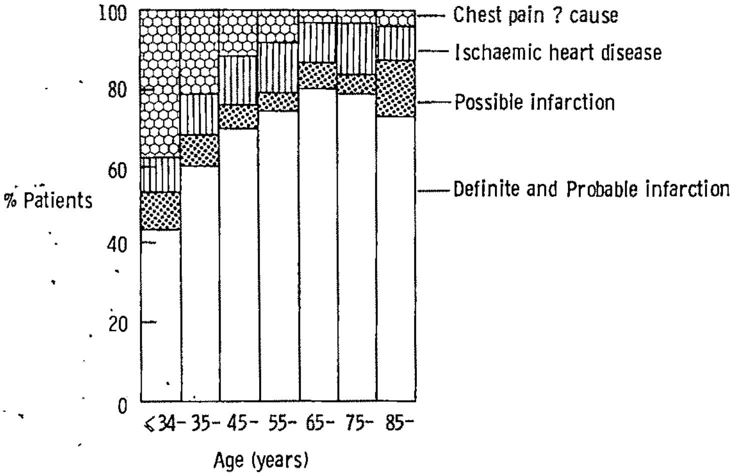

Fig. *Percentage of patients in each age group with the different diagnostic categories of heart attack.*

the first call for help among patients who reached hospital alive than among those who were found dead on arrival. Table 2 shows the intervals between the onset of symptoms and the call for an ambulance in the patients who were admitted to hospitals and in whom the duration of the symptoms was known (96·4% of those admitted). There was no difference between the age groups, 50 per cent of each group having called for help by between one and a half and four hours after the onset of symptoms. The time taken for an ambulance to respond to the call and to transport the patient to hospital was also similar in each group, and there was nothing to suggest that elderly people were handled with less urgency than younger ones.

(2) HOSPITAL EVENTS

The Figure shows that with increasing age the proportion of patients eventually found to have had definite, probable, or possible myocardial infarctions increased progressively from 54 per cent in those aged 34 or less, to 87 per cent in those aged 85 or more. The proportion of patients eventually considered to have ischaemic heart disease without infarction varied from 9 to 14 per cent without any age-related pattern, but the proportion of patients in whom no adequate cause of chest pain could be found fell from 36 per cent in the youngest patients to 4 per cent in the oldest.

Table 3 shows the number of people in each age group who were admitted to hospital, who had a diagnosis of definite or probable myocardial infarction, and who died from their infarction. The fatality rates from myocardial infarction show a small increase to age 64 years, and a pronounced increase thereafter. The death rate from myocardial infarction was 31 per cent in patients aged 65 years or more, and 16 per cent in those aged 64 years or less. Patients aged 65 or more accounted for 35 per cent of all admissions, 38 per cent of all infarctions, and 55 per cent of all the deaths from infarction.

The proportion of patients known to have had previous myocardial infarction varied from 8 to 31 per cent in the different age groups (mean for all ages, 28%), and there was no age-related trend. Similarly there was no age-related pattern of difference in the numbers of patients recorded as complaining of chest pain (87 to 96% in the different age groups) or of breathlessness (38 to 58%). Table 4 shows that there was no age-related pattern in the

Table 3 *Number of patients in each age group who were admitted to hospital, number who had definite or probable myocardial infarction, and % deaths among those with either definite or probable infarction*

Age group	*≤34*	*35–*	*45–*	*55–*	*65–*	*75–*	*85–*	*Total*
Number of patients	22	133	499	697	549	160	23	2083
Patients with definite or probable infarction	12	92	381	550	472	132	20	1659
Deaths in hospital	1	16	48	98	138	51	7	359
Deaths as % of patients with definite or probable infarction	8	17	13	18	29	39	35	22

Table 4 *Electrocardiographic position of infarction in patients with definite or probable myocardial infarction*

Age group	*≤34*	*35–*	*45–*	*55–*	*65–*	*75–*	*85–*	*Total*
Number of patients	12	92	381	550	472	132	20	1659
Percentage with anterior or lateral infarction	83	47	48	51	47	52	35	49
Percentage with inferior or posterior infarction	17	37	42	39	33	24	25	37
Percentage with no definite electrocardiographic evidence of infarction	0	16	10	10	20	24	40	14

proportion of patients of different ages with anterior infarctions on the electrocardiogram but a slightly lower proportion of the older patients had inferior infarcts. Table 5, however, shows that with increasing age more patients were found to have raised jugular venous pressure, peripheral oedema, basal lung crepitations, or an arrhythmia of some kind. Elderly patients were more often given digoxin and diuretics than younger ones.

The average duration of hospital stay in the whole group was 10 days. Nine per cent of those aged 75 to 84, and 16 per cent of those aged 85 or over, stayed in hospital more than three weeks, but less than 5 per cent in all other age groups were kept in hospital for this length of time.

Discussion

If an ambulance is called to a patient with suspected myocardial infarction the patient's chances of dying depend on his age. There are more prehospital deaths among old people than among young ones, and there is a higher hospital mortality from myocardial infarction among the elderly. Though we collected data on all the patients transported to hospital by ambulance, ours was not a complete community study, for we have no information about the patients who had undiagnosed myocardial infarction and survived, or who had fatal infarction, death being certified by a general practitioner who summoned a hearse rather than an ambulance, or about those in whom infarction was diagnosed but who were treated at home. Nevertheless, our results are similar to those of smaller studies where all cases of myocardial infarction have been registered.[8]

It is clear that the effect of age on mortality is not caused by the behaviour of the patients or their doctors. In all age groups except the very old about two-thirds of patients were at home when they developed their symptoms. Similar proportions of each age group called for help from a general practitioner. The delay between onset of symptoms and a call for help was not affected by age, nor did it alter the speed of the response by the ambulance. We have previously shown that though old people are less likely to be admitted to a coronary care unit than young ones, this does not influence mortality.[9]

The only things that seem to characterise the elderly patients with myocardial infarction are greater frequencies of heart failure and arrhythmias than in the younger ones. The increasing frequency of heart failure in the older age groups might be related to the increasing fatality rate with age in one of two ways. First, older people may suffer more myocardial damage than young ones when an infarction occurs, so that the infarction causes both a higher fatality rate and an increased incidence of heart failure in those who survive. Alternatively, older people may be more likely than younger ones to have pre-existing heart failure from a variety of causes, so that an infarction is less well tolerated.

A district general hospital that admits all types of patients with heart attacks is likely to deal with many more elderly people than a specialist cardiac centre, to which young patients will almost certainly be selectively referred. There is little convincing evidence that during the past 10 years hospital

Table 5 *Percentage of patients in different age groups with various clinical signs on admission, percentage in whom arrhythmias were detected, and percentage given digoxin and diuretics during hospital stay*

Age group	*≤34*	*35–*	*45–*	*55–*	*65–*	*75–*	*85–*
Number of patients	22	133	499	697	549	160	23
Percentage with raised jugular venous pressure	9	10	11	19	22	30	33
Percentage with peripheral oedema	0	1	6	5	14	20	35
Percentage with any arrhythmia	22	25	26	32	38	32	52
Percentage given digoxin	27	20	22	35	37	46	39
Percentage given diuretics	27	21	36	49	56	70	43

admission has led to a real reduction in mortality rates from myocardial infarction[10] and claims of very low fatality rates from specialist centres must be regarded with caution unless detailed information is provided about the age of the patients treated.

References

1 Peel AAF. Age and sex factors in coronary artery disease. *Br Heart J* 1955; **17:** 319–26.

2 Pell S, D'Alonzo CA. Immediate mortality and five-year survival of employed men with a first myocardial infarction. *N Engl J Med* 1964; **270:** 915–22.

3 Norris RM, Caughey DE, Mercer CJ, Scott PJ. Prognosis after myocardial infarction: six year follow up. *Br Heart J* 1974; **36:** 786–90.

4 Kitchin AH, Pocock SJ. Prognosis of patients with acute myocardial infarction admitted to a coronary care unit: I. survival in hospital. *Br Heart J* 1977; **39**; 1163–6.

5 Henning H, Gilpin EA, Covell JW, Swan EA, O'Rourke RA, Ross J Jr. Prognosis after acute myocardial infarction: a multivariate analysis of mortality and survival. *Circulation* 1979; **59:** 1124–36.

6 O'Rourke MF, Walsh B, Fletcher M, Crowley A. Impact of the new generation coronary care unit. *Br Med J* 1976; **iii:** 837–9.

7 Chapman BL. Effect of coronary care on myocardial infarct mortality. *Br Heart J* 1979; **42:** 386–95.

8 Tunstall-Pedoe H. Uses of coronary heart attack registers. *Br Heart J* 1978; **40:** 510–15.

9 Hill JD, Holdstock G, Hampton JR. Comparison of mortality of patients with heart attacks admitted to a coronary care unit and an ordinary medical ward. *Br Med J* 1977; **ii:** 81–83.

10 Rose G. The contribution of intensive coronary care. *Br J Prev Soc Med* 1975; **29:** 147–50.

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Changes in red cell deformability and other haemorrheological variables after myocardial infarction

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SUMMARY Haemorrheological variables were studied in 43 patients after acute myocardial infarction. Red cell deformability, by a filtration method, was significantly lower within 12 hours of infarction than subsequently. This drop was greater in the presence of haemodynamic complications. Blood viscosity, particularly when adjusted to a standard haematocrit, rose in the week after infarction, as did plasma viscosity and plasma fibrinogen. Haematocrit, however, fell over this period. These changes could increase myocardial ischaemia and lead to extension of the area of infarction.

Myocardial infarction is an important cause of death in Western communities.[1] Though there is still disagreement on the pathogenesis of the vascular occlusion, current interest lies in limiting the ultimate size of the infarct by preventing extension into the surrounding area of marginal ischaemia. Changes in the physical flow properties of blood may have an important influence on blood flow and oxygen supply to ischaemic myocardium.[2] The purpose of this study was to examine the changes in red cell deformability and other haemorrheological variables after acute myocardial infarction.

Patients and methods

Forty-three patients with myocardial infarction (35 men, eight women; age range 33 to 76 years; mean age 58·6 years) admitted consecutively to the intensive care unit were studied. Requirements for a diagnosis of myocardial infarction were two or more of the following: (a) typical history; (b) an increase in the serum aspartate transaminase or serum hydroxybutyrate dehydrogenase concentration to more than twice the upper limit of normal within three days of admission; and (c) characteristic evolutionary electrocardiographic abnormalities.

Samples of blood were drawn from an antecubital vein using a 21 G needle without cuff occlusion: 20 ml was anticoagulated with solid lithium heparin (12·5 units/ml) for rheological studies and 5 ml with 0·5 ml of 3·8 per cent trisodium citrate solution for plasma fibrinogen estimation. Collections were made one, three, five, and 10 days after the presumed infarction indicated by the history. Samples were not collected at weekends,

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Table *Haemorrheological variables after myocardial infarction (mean ± SEM)*

	Day 0	*Day 1*	*Day 3*	*Day 5*	*Day 10*
Blood viscosity 0·77/s (mPa/s)	26·7 ±2·1	29·6 ±1·5	31·7 ±1·4	29·6 ±1·4	28·6 ±1·0
Blood viscosity (C) 0·77/s (mPa/s)	26·3 ±1·5	30·1 ±1·0*	33·9 ±0·9‡	33·9 ±1·2‡	32·8 ±1·0***
Blood viscosity 2·62/s (mPa/s)	15·3 ±1·1	16·8 ±0·6	16·6 ±0·7	16·6 ±0·6	16·3 ±0·7
Blood viscosity (C) 2·62/s (mPa/s)	14·5 ±0·7	16·7 ±0·4***	17·3 ±0·4***	18·0 ±0·6‡	17·8 ±0·5‡
Blood viscosity 91/s (mPa/s)	4·8 ±0·2	4·8 ±0·1	5·0 ±0·1	4·8 ±0·2	4·7 ±0·1
Blood viscosity (C) 91/s (mPa/s)	4·7 ±0·1	4·9 ±0·1	5·1 ±0·1*	5·1 ±0·1*	5·1 ±0·1*
Plasma viscosity (mPa/s)	1·41 ±0·03	1·45 ±0·02	1·52 ±0·02***	1·54 ±0·02†	1·60 ±0·02‡
Haematocrit (%)	45·0 ±1·1	44·0 ±0·9	43·1 ±0·7	41·7 ±0·6**	41·3 ±0·7**
Plasma fibrinogen (g/l)	4·3 ±0·3	4·6 ±0·2	6·3 ±0·2‡	6·9 ±0·3‡	6·3 ±0·3‡
Deformability index	0·22 ±0·04	0·49 ±0·05‡	0·55 ±0·03	0·56 ±0·03‡	0·63 ±0·02‡
n	17	33	39	38	36

(C) adjusted to a standard haematocrit (45%).
* $p < 0·05$. ** $p < 0·02$. *** $p < 0·01$. † $p < 0·005$. ‡ $p < 0·001$ when compared with day 0.

and some final samples were not collected because of death or discharge from hospital. Seventeen patients had an additional sample drawn within 12 hours of infarction (day 0).

Red cell deformability was assessed by a filtration method previously described[3] in which a 5 per cent suspension of red cells in autologous prefiltered plasma was passed through individual 5 μm Nuclepore polycarbonate sieves (Nuclepore Corporation, Pleasanton, California, USA). The deformability index was defined as the fraction of 1 ml of this suspension filtered in 60 s.

Whole blood viscosity at shear rates of 0·77/s, 2·62/s, and 91/s together with plasma viscosity were measured at 37°C using a Contraves low shear 2 rheometer.[4] The results were also adjusted to a standard haematocrit of 45 per cent.[4] Plasma fibrinogen by a clot weight method,[5] and microhaematocrit were also measured.

Student's t test (two-tailed) was used for statistical analysis.

Results

The results for the whole group are contained in the Table. Red cell deformability was lowest on day 0, rising significantly by day 1, with small increases thereafter (p < 0·001) (Fig. 1). The earliest deformability index determined (day 0 or 1) was lower in 11 patients with radiological alveolar or interstitial pulmonary oedema on admission (0·22 ± 0·07 SEM) than in patients without oedema (0·47 ±0·05 SEM) (p < 0·01) (Fig. 2). Five patients with cardiogenic shock (systolic blood pressure < 100 mmHg, cool peripheries, oliguria) had lower earliest deformability indices (0·11 ±0·04 SEM) than those without shock (0·44 ±0·05 SEM) (p < 0·02). Three of those with shock died within two weeks of infarction (indices 0, 0, 0·22).

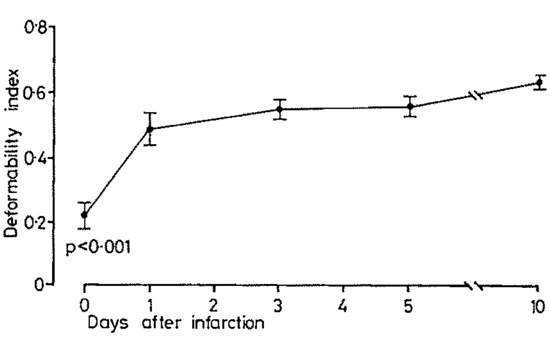

Fig. 1 *Change in red cell deformability after myocardial infarction (mean ±SEM). The day 0 value is significantly different from the values on all other days.*

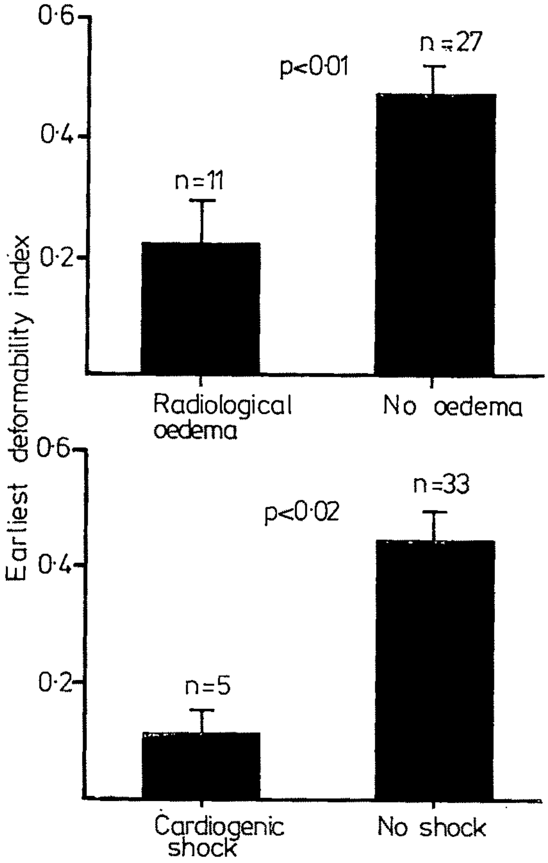

Fig. 2 *Earliest deformability indices in those with radiological pulmonary oedema on admission compared with those without oedema and those with cardiogenic shock compared with those not shocked (mean ±SEM).*

Whole blood viscosity, when adjusted to a standard haematocrit, increased significantly by the third day at each of the three shear rates. The greatest increase occurred at the lowest shear rate, where there was a 29 per cent rise over the initial reading. Plasma fibrinogen and plasma viscosity also showed significant increases by the third day. Haematocrit, however, decreased, being 10 per cent lower on the fifth day. Whole blood viscosity without correction for haematocrit did not change at the highest shear rate and showed only insignificant rises at the other shear rates.

Patients sampled on day 0 did not appear to be a select group because they did not differ significantly from other patients in peak cardiac enzyme concentrations or in the haemorrheological values measured on the subsequent days.

Discussion

Myocardial ischaemia has been associated with abnormal blood rheology in a number of reports.[6 7] After myocardial infarction, whole blood viscosity, plasma viscosity, and plasma fibrinogen have been shown to be raised.[8 9] In previous reports red cell deformability has only been assessed by a viscometric method.[9] We have chosen microfiltration which we believe to be a better model of the microcirculation. Further, we have used red cells resuspended in autologous plasma to include the influence of plasma proteins and other plasma factors on red cell deformability.

In this study we have confirmed previous observations on the changes in blood viscosity after myocardial infarction. A significant increase in whole blood viscosity at low shear rate was found when adjusted to a standard haematocrit. The rise in whole blood viscosity, however, at the low shear rate when not adjusted for haematocrit did not quite reach significance. The explanation appeared to be the opposing influences of a rise in plasma fibrinogen and a fall in haematocrit. A reduction in haematocrit will lead to a reduction in blood viscosity whereas a rise in plasma fibrinogen concentration will increase red cell aggregation, and thus increase blood viscosity measured at low shear rates.[4] Increased blood viscosity could well alter blood flow and oxygen delivery to ischaemic myocardium.[2] It is now established that an area of ischaemic tissue exists around a central area of infarction.[10] Maintenance of blood flow to this region may be crucial in limiting the ultimate infarct size. As blood flow in the coronary circulation is predominantly diastolic, and thus over a relatively small pressure difference, even a small increase in blood viscosity at low shear rates could further reduce flow.[2 11]

The most striking observation in this study is the low red cell deformability, as indicated by the reduced proportion of red cells able to pass a 5 μm filter, during the first 12 hours after myocardial infarction. This phenomenon was most pronounced in the presence of haemodynamic complications, particularly cardiogenic shock. Factors other than red cell deformability that might impair filtrability of red cells are unlikely to explain this finding. Buffy coat removal and plasma filtration before resuspension of cells avoid filter plugging by leucocytes. Use of a dilute red cell suspension minimises red cell interaction and resulting rouleaux or aggregates. Indeed, were the latter a major factor, the increased aggregability by day 3, indicated by the rise in whole blood viscosity at the lowest shear rate after correction to a standard haematocrit, would have further impaired filtrability. In fact the filtration of red cells had returned to almost normal by the third day, supporting the concept that filtration changes primarily reflect changes in red cell deformability. In vivo, normal deformability allows red cells, whose greater diameter usually exceeds 7 μm, to pass through segments of capillaries as narrow as 3 μm in diameter.[12] A reduction in deformability could lead to impaired perfusion in the microcirculation and this may be particularly important in an area of myocardial ischaemia where acidosis would further impair red cell deformability.[12]

The changes we have described are most likely to be secondary and not related to the pathogenesis of the infarct. They could well aggravate the ischaemia in the myocardium, however, and lead to extension of the area of infarct. Treatment designed to prevent or reduce these effects may be an approach to explore in the immediate management of myocardial infarction.

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References

1 World Health Organisation. World Health Statistics Annual. Vol. 1: *Vital statistics and causes of death.* Geneva: World Health Organisation, 1977.
2 Gordon RJ, Snyder GK, Tritel H, Taylor WJ. Potential significance of plasma viscosity and hematocrit variations in myocardial ischemia. *Am Heart J* 1974; **87**: 175–82.
3 Dodds AJ, O'Reilly MJG, Yates CJP, Flute PT, Dormandy JA. Haemorrheological response to plasma exchange in Raynaud's phenomenon. *Br Med J* 1979; **ii**: 1186–7.
4 Dormandy JA. Mechanical and engineering problems of blood viscosity. *Biomed Eng* 1974; **9**: 284–303.
5 Ingram GIC. The determination of plasma fibrinogen by clot weight method. *Biochem J* 1952; **51**: 583–5.
6 Burch GE, DePasquale NP. Hematocrit, blood viscosity and myocardial infarction. *Am J Med* 1962; **32**: 161–3.
7 Nicolaides AN, Bowers R, Horbourne T, Kidner PH, Besterman EM. Blood viscosity, red-cell flexibility, haematocrit, and plasma fibrinogen in patients with angina. *Lancet* 1977; **ii**: 943–5.
8 Fulton RM, Duckett K. Plasma-fibrinogen and thromboemboli after myocardial infarction. *Lancet* 1976; **ii**: 1161–4.
9 Jan KM, Chien S, Bigger JT Jr. Observations on

blood viscosity changes after acute myocardial infarction. *Circulation* 1975; **51:** 1079–84.

10 Maroko PR, Braunwald E. Modification of myocardial infarction size after coronary occlusion. *Ann Intern Med* 1973; **79:** 720–33.

11 Salisbury PF, Cross CE, Rieben PA. Acute ischemia of inner layers of ventricular wall. *Am Heart J* 1963; **66:** 650–6.

12 Anonymous. Red cell deformability (leading article). *Lancet* 1978; **ii:** 1348–9.

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R wave amplitude during exercise

Relation to left ventricular function and coronary artery disease

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SUMMARY Change in R wave amplitude (mean ΔR) was measured sequentially during and after 12 lead maximal treadmill exercise tests in 14 subjects with normal coronary arteries and 62 patients with coronary artery disease. In normal subjects mean ΔR decreased maximally one minute after exercise and returned to control levels within three minutes. In contrast, meanΔR increased in patients with coronary artery disease, the greatest change occurring in patients with either triple vessel or left main disease or those with an akinetic region on the left ventriculogram. R wave amplitude returned to resting levels in five minutes. Increase in R wave amplitude was not directly related to changes in the ST segment.

Changes in R wave amplitude during maximal treadmill exercise may improve the discrimination between patients with and without coronary artery disease and may help to identify those patients with abnormal left ventricular function.

Mathematical models of electrical activity of the heart predict that changes in intraventricular volume will be associated with changes in R wave amplitude measured by the surface electrocardiogram, an increase or a decrease of volume giving rise to a corresponding change of R wave amplitude.[1–3] Animal experiments when intraventricular volume was manipulated by acute haemorrhage and overtransfusion have confirmed this prediction.[4] In man similar observations have been reported after acute surgical blood loss.[5]

More recently, changes in R wave amplitude have been studied during exercise.[6–8] Measured in a single electrocardiographic lead, R wave amplitude decreased in normal subjects while an increase or no change was seen in patients with coronary artery disease. These investigators concluded that R wave amplitude criteria, in conjunction with ST segment depression, improved both the sensitivity and specificity of exercise testing.

The purpose of this study was to measure R wave amplitude during and after maximal 12 lead treadmill exercise and to evaluate the relation of changes to the severity of coronary artery disease and to abnormalities of left ventricular contraction.

Patients and methods

Seventy-six patients, referred to the National Heart Hospital for chest pain, underwent both maximal treadmill exercise testing and coronary angiography. The following patients were excluded: those with valvular heart disease, primary myocardial disease, conduction defects, or those on digitalis; those with technically inadequate stress tests and those who failed to complete the exercise test.[9 10]

Fourteen patients (nine men, five women, mean age 38 years) had normal coronary angiograms and normal resting electrocardiograms; 62 patients (50 men, 12 women, mean age 48 years) had coronary artery disease proven at angiography. Twenty-eight of these (45%) had a history of myocardial infarction and pathological Q waves in the resting electrocardiogram.

EXERCISE TEST

All patients underwent 12 lead maximal treadmill exercise testing[11] within one month of coronary

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angiography. The 12 leads recorded were the same as a standard 12 lead resting electrocardiogram except that the limb leads were sited on the trunk close to the limb in question. Recordings were made in the erect position, before, and at the end of each three minute stage of exercise, and at one minute intervals after exercise in the sitting position until the electrocardiogram returned to its resting state. The test was terminated when predicted maximum heart rate for age, sex, and weight (women) or height (men) had been achieved, or with the onset of chest pain associated with electrocardiographic changes. Patients who failed to reach either of these end points were excluded. The Bruce protocol was used with the addition of a warm-up stage at 1·0 mph and 5 per cent gradient to avoid the sudden increase in oxygen consumption during stage 1 of the unmodified Bruce protocol.[12] Horizontal or downsloping ST segment depression of 1 mm or more persisting for 80 ms beyond the J point in at least one lead was regarded as a positive test for ischaemia (calibration 10 mm = 1 mV). Electrocardiographic recordings were made with a fully automated three channel Cambridge 3038 portable electrocardiographic recorder.* The frequency response was 0·05 to 100 Hz (–3dB), with the time constant (67% loss of amplitude) greater than 3·2 s. Recording equipment and procedures complied with American Heart Association standards.[13 14] Blood pressure measurements were taken before each electrocardiographic recording before, during, and after exercise.

R wave amplitude was measured by two observers without prior knowledge of or reference to the results of angiography. The amplitude was measured in mm (10 mm = 1 mV) from the PQ segment to the top of the R wave and averaged in each individual lead over four to 10 beats, depending on heart rate, to minimise the effect of respiration. Leads II, III, aVF, V4–6 were chosen for detailed analysis as they usually had dominant R waves. Results are expressed as the mean change in R wave amplitude (mean ΔR) which is calculated by subtracting the sum of R waves in the six leads from the pre-exercise value and then dividing by six. A mean ΔR of –2 mm would therefore reflect a total 1·2 mV decrease in the six leads. In a separate group of eight normal volunteers who underwent two exercise tests changes in mean ΔR were reproducible.

CORONARY ANGIOGRAPHY

Left ventriculography was performed in the 30° right anterior oblique projection. Left ventricular wall motion was assessed subjectively by two independent observers and reported as normal, hypokinetic (defined as reduced inward systolic movement), or akinetic (defined as absent inward systolic movement). Coronary angiography was performed in the posteroanterior and oblique projections using the Sones technique. Seventy per cent reduction in the diameter of a major coronary artery was considered significant.

Results are expressed as mean ± the standard error of the mean. Statistical tests were performed using Student's t test for paired and non-paired samples and by linear regression.

Results

A typical example of a standard 12 lead electrocardiographic response to maximal treadmill exercise in a normal subject is shown in Fig. 1. The absence of pathological ST change and decrease in R wave voltage (most obvious in the inferolateral leads) may be seen.

For comparison, a positive test, from a patient with triple vessel disease, is shown in Fig. 2. ST depression occurred in most leads and R wave amplitude increased. However, ST depression in leads, I, aVL, and V2–3 was not accompanied by R wave change, indicating that this can be independent of ST segment change in an individual lead.

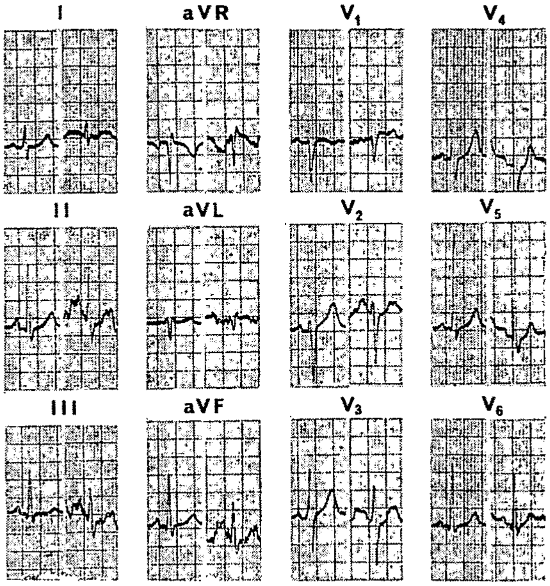

Fig. 1 *Paired 12 lead resting* (left) *and maximal exercise* (right) *electrocardiographic complexes from a normal subject. Decrease in R wave amplitude is most pronounced in leads II, III, aVF, and V4–6.*

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* Cambridge Instrument Company.

Of the 76 patients, 59 had positive and 17 negative exercise tests as judged by ST segment analysis. There were two false positives and five false negatives, giving a sensitivity of 92 per cent and specificity of 86 per cent (Table). All 14 patients with normal coronary arteries had normal left ventriculography, and R wave amplitude decreased during exercise (Fig. 3). The maximum fall of mean ΔR occurred one minute after exercise and returned to the pre-exercise value within three minutes. Maximum change in heart rate preceded maximum change in mean ΔR and recovered more slowly than R wave amplitude.

The 62 patients with coronary artery disease comprised 22 with single vessel, 12 with double vessel, and 28 with triple vessel or left main disease. Left ventriculography was normal in 28. Eighteen patients had a region of hypokinesia and 16 akinesia. Sixty-one patients (98%) had an increase in mean ΔR. The one patient showing a decrease in mean ΔR had single vessel disease, a negative exercise test, and normal left ventriculography. The four other patients with false negative exercise tests also had single vessel disease. Fig. 4 shows the change in mean ΔR related to the severity of coronary artery disease. In contrast to normal

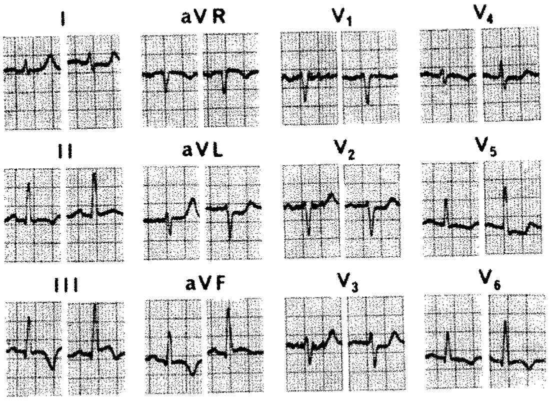

Fig. 2 *Paired 12 lead resting* (left) *and maximal exercise* (right) *electrocardiographic complexes from a patient with severe triple vessel coronary artery disease and inferior wall hypokineses. R wave voltage increase is most distinct in leads II, III, aVF, and V4–6, and occurs in the presence of both ST depression (V2–5) and elevation (II, III, aVF).*

Table *Sensitivity (true positive tests/no. of patients with coronary artery disease) and specificity (true negative/no. of patients with normal coronary angiography) of treadmill exercise testing*

	ST analysis	*R wave amplitude*
Sensitivity	92% (57/62)	98% (61/62)
Specificity	86% (12/14)	100% (14/14)

In column 1 a positive test is defined as flat or downsloping ST depression of 1 mm or more 80 ms after the J point; in column 2 a positive test is defined by no change or an increase in R wave amplitude at maximal exerise compared with the resting value.

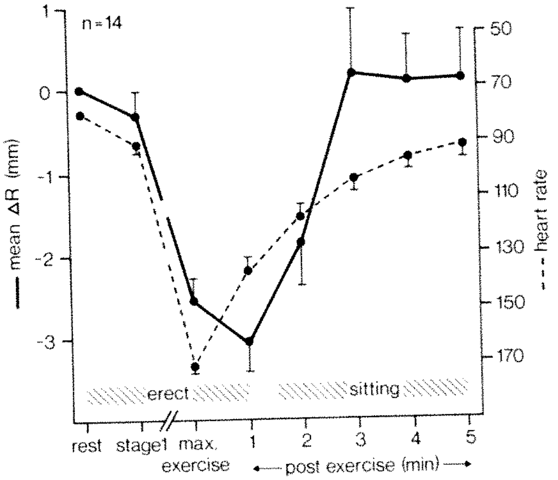

Fig. 3 *Heart rate and mean change in R wave amplitude (ΔR) in 14 normal subjects during treadmill exercise. ΔR decreases most at one minute after exercise and returns to resting level three minutes after exercise.*

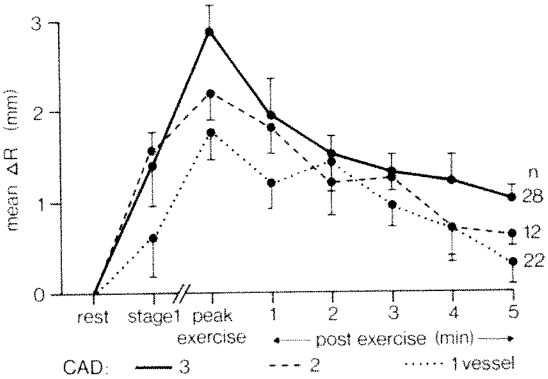

Fig. 4 *Exercise-induced change of R wave amplitude in patients with coronary artery disease. ΔR does not distinguish the number of vessels involved except between triple vessel disease (3) and double (2) or single (1) vessel disease at peak exercise* ($p < 0{\cdot}01$).

patients (Fig. 3) mean ΔR increased. The maximum increase occurred at peak exercise and mean ΔR returned to resting values five minutes after exercise. The change in mean ΔR was not influenced by the number of diseased coronary arteries except at peak exercise when mean ΔR was greater in patients with triple vessel or left main disease than with single vessel disease ($p < 0{\cdot}01$).

Fig. 5 shows the change in mean ΔR related to abnormality of left ventricular contraction. The largest increase in mean ΔR occurred in those patients with akinetic regions of the left ventricle and remained statistically significant up to 5 minutes ($p < 0{\cdot}001$).

There was no significant correlation between the mean ΔR and both the number of leads showing ST depression and the sum of ST depression seen in all 12 leads (Fig. 6). Patients with multiple vessel disease, however, had higher values of both mean ΔR and ΣST (Fig. 7).

Discussion

The precise mechanism for the change in R wave amplitude on the surface electrocardiogram during exercise is unclear. R wave amplitude changes under a variety of conditions and is influenced by many factors such as blood conductivity, blood potassium, electrical axis, and movement of the chest wall and diaphragm. Several experimental and theoretical studies$^{1-5\ 15-19}$ indicate that a major determinant of R wave amplitude is the intraventricular volume. The end-diastolic volume of the left ventricle decreases during exercise in normal subjects$^{20-25}$ while at the same time R wave amplitude decreases.$^{7\ 26-32}$ These two phenomena may therefore be directly related.

Many studies using different techniques have shown that during acute ischaemia the end-diastolic left ventricular volume does not decrease but increases.$^{23\ 24\ 33-37}$ Our results show that R wave

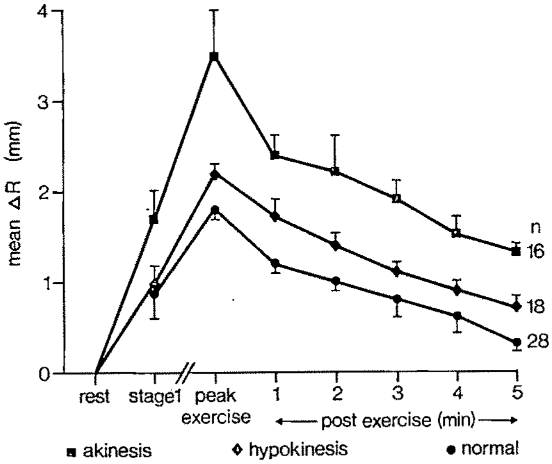

Fig. 5 *Exercise-induced change in R wave amplitude in the 62 patients with coronary artery disease, subdivided according to the result of left ventriculography. Patients with akinesis demonstrated significantly greater increase which took longer to return to resting values than the others.*

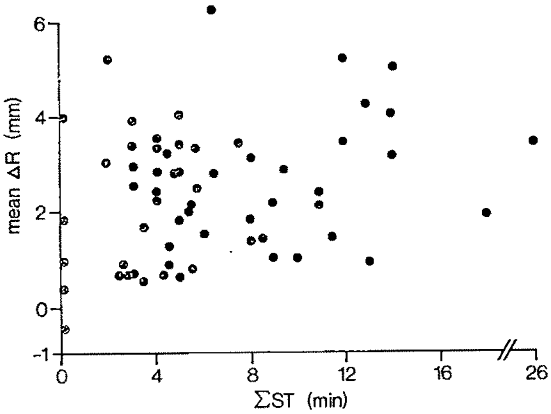

Fig. 6 *Plot of the sum of ST segment depression on the 12 lead electrocardiogram (ΣST) and change in mean R wave amplitude (ΔR) at peak exercise in 62 patients with coronary artery disease. There is no significant correlation.*

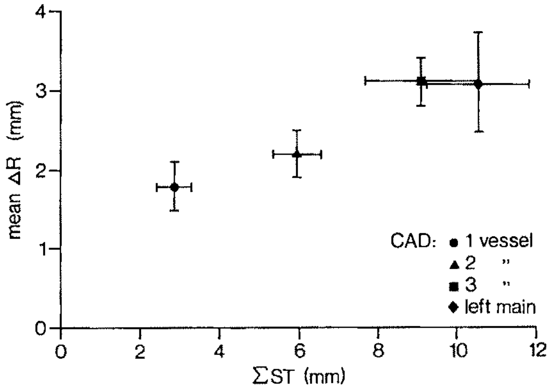

Fig. 7 *Sum of ST segment depression on the 12 lead electrocardiogram (ΣST) at peak exercise and mean increase in R wave amplitude (ΔR) in 62 patients with coronary artery disease (CAD). ΣST shows better distinction between the groups than ΔR.*

amplitude is also increased in those patients with coronary artery disease in contrast to normal subjects (Fig. 3 and 4). If R wave changes are attributable to volume change, a correlation between R wave amplitude and left ventricular contraction abnormalities should exist. Our results confirm this prediction and show that within the group of patients with coronary artery disease the size of the change in R wave amplitude relates to the findings of ventriculography (Fig. 5) rather than to the number of diseased vessels (Fig. 4). Yet even in the subgroup of patients with coronary artery disease and normal left ventriculography R wave amplitude increased; this is presumably because abnormalities of ventricular contraction, though not apparent at rest, occur on exercise with the onset of ischaemia. No distinct correlation was found between changes in R wave amplitude and ST segment depression (Fig. 6), though patients with three vessel disease or disease of the left main coronary artery had larger increases of R wave amplitude and greater ST depression than the others (Fig. 7). Thus ST segment changes may reflect the electrophysiological consequence of ischaemia while R wave amplitude is primarily affected by left ventricular volume.

Our results with regard to R wave amplitude during exercise are in accord with the findings of others.[7 8 28 29] There are, however, three recent reports in which R wave amplitude did not distinguish between patients with and without coronary artery disease. Battler *et al.*[30] using a different lead system, supine bicycle exercise, and radionuclide angiography found QRS amplitude to be of no value in separating a normal from an abnormal exercise response.

Wagner *et al.*[32] though showing a decreased R wave amplitude in their normal subjects concluded that it was unreliable in distinguishing the presence, absence, or severity of coronary artery disease. In contrast to our study, however, they used only two leads (II and V5) for analysis, employed submaximal exercise, and studied a group of patients having a preponderance of single vessel disease. In a group of patients with significant but unspecified coronary artery disease, Fox *et al.*[38] using erect bicycle exercise and praecordial surface mapping found a consistent decrease in R wave amplitude in patients with or without electrocardiographic evidence of ischaemia. The reasons for these opposite or less clear-cut findings may be related to differences in the patients under study, the type of exercise, posture during exercise, and the recording leads selected.

In an attempt to improve the sensitivity and specificity of exercise testing we redefined all tests as positive or negative according to the results of R wave analysis (Table). Thus, a positive (abnormal) test would be one in which R wave amplitude shows either no change or an increase at maximal exercise, and a negative (normal) response would be a demonstrable decrease in R wave amplitude. Four of the five false negatives and both false positives (by ST analysis) are correctly classified as abnormal and normal, respectively, in this way. Though our series is relatively small we agree with the conclusions of Bonoris *et al.*[6] that, while in no way superseding the value of ST segment analysis, evaluation of R wave amplitude should not be ignored and may help separate patients with coronary artery disease from those without such disease. We are currently using both ST segment and R wave amplitude criteria prospectively to confirm these results.

Our results are impressively accurate but probably no more or less than expected for a selected group of patients referred with chest pain to a specialist hospital.[39] A larger group of patients needs to be studied before any definite claim can be made with regard to the clinical value of this observation or the possible advantages in studying a population with a low prevalence of coronary artery disease. In such a population the requirement that a normal exercise test be accompanied by a fall in R wave amplitude should improve the specificity of exercise testing.

Lastly, since R wave amplitude change with exercise appears to be related to an abnormality of left ventricular contraction, analysis of R wave change may provide a non-invasive indicator of left ventricular function, helping to identify those patients in whom it is more likely to be impaired.

References

1 Brody DA. A theoretical analysis of intracavity blood mass influence on the heart-lead relationship. *Circ Res* 1956; **4:** 731–8.
2 Nelson CV, Chatterjee M, Angelakos ET, Hecht HH. Model studies on the effect of the intracardiac blood on the electrocardiogram. *Am Heart J* 1961; **62:** 83–92.
3 Bayley RH, Kalbfleisch JM, Berry PM. Changes in the body's QRS surface potentials produced by alterations in certain compartments of the nonhomogeneous conducting model. *Am Heart J* 1969; **77:** 517–28.
4 Manoach M, Gitter S, Grossman E, Varon D, Gassner S. Influence of hemorrhage on the QRS complex of the electrocardiogram. *Am Heart J* 1971; **82:** 55–61.
5 Scherf D, Bornemann C. The electrocardiogram after acute hemorrhage. *Dis Chest* 1968; **53:** 99–100.
6 Bonoris PE, Greenberg PS, Christison GW, Castellanet MJ, Ellestad MH. Evaluation of R wave

amplitude changes versus ST-segment depression in stress testing. *Circulation* 1978; **57:** 904–10.

7 Bonoris PE, Greenberg PS, Castellanet MJ, Ellestad MH. Significance of changes in R wave amplitude during treadmill stress testing: angiographic correlation. *Am J Cardiol* 1978; **41:** 846–51.

8 Christison GW, Bonoris PE, Greenberg PS, Castellanet MJ, Ellestad MH. Comparison of changes in R-wave amplitude (RWA) and ST segments in treadmill stress testing (TST) as a predictor of CAD (abstract). *Am J Cardiol* 1978; **41:** 376.

9 Linhart JW, Turnoff HB. Maximal treadmill exercise test in patients with abnormal control electrocardiograms. *Circulation* 1974; **49:** 667–72.

10 Kattus AA. Exercise electrocardiography: recognition of the ischemic response, false positive and negative patterns. *Am J Cardiol* 1974; **33:** 721–31.

11 Baron D, Poole-Wilson PA, Rickards AF. Maximal 12 lead treadmill test for prediction of severity of coronary artery disease. *Eur J Cardiol* 1980; **11:** 259–67.

12 Bruce RA. Exercise testing of patients with coronary heart disease. *Ann Clin Res* 1971; **3:** 323–32.

13 Ellestad MH, Blomqvist CG, Naughton JP. Standards for adult exercise testing laboratories. *Circulation* 1979; **59:** 421A–8A.

14 Hellerstein HK. Specifications for exercise testing equipment. *Circulation* 1979; **59:** 849A–54A.

15 Lepeschkin E. Physiological factors influencing the electrocardiographic response to exercise. In: Blackburn H, ed. *Measurements in exercise electrocardiography. The Ernst Simonson Conference.* Springfield, Illinois: Charles C Thomas, 1969: 363.

16 Lab MJ. Is there mechano-electric transduction in cardiac muscle? *S Afr J Med Sci* 1968; **33:** 60.

17 Manoach M, Grosman E, Varon D, Gitter S. QRS amplitude changes during heart filling and digitalization (letter). *Am Heart J* 1972; **83:** 292–5.

18 Millard RW, Hodgkin BC, Nelson CV. End-diastolic volume changes reflected in the electrocardiogram (abstract). *Circulation* 1974; **50,** suppl III: 192.

19 Hugenholtz PG, Nelson CV, Angelakas ET. Effects of intracardiac blood on the spatial vectorcardiogram (abstract). *Trans Eur Soc Cardiol* 1978; **1:** 278.

20 Braunwald E, Goldblatt A, Harrison DC, Mason DT. Studies on cardiac dimensions in intact, unanesthetized man. III Effects of muscular exercise. *Circ Res* 1963; **13:** 460–7.

21 Braunwald E, Sonnenblick EH, Ross J Jr, Glick G, Epstein SE. An analysis of the cardiac response to exercise. *Circ Res* 1967; **20,** suppl I: 44–58.

22 Vatner SF, Pagani M. Cardiovascular adjustments to exercise: hemodynamics and mechanisms. *Prog Cardiovasc Dis* 1976; **19:** 91–108.

23 Sharma B, Goodwin JF, Raphael MJ, Steiner RE, Rainbow RG, Taylor SH. Left ventriculography on exercise. A new method of assessing left ventricular function in ischaemic heart disease. *Br Heart J* 1976; **38:** 59–70.

24 Nichols AB, Strauss HW, Moore RH, *et al.* Acute changes in cardiopulmonary blood volume during upright exercise stress testing in patients with coronary heart disease. *Circulation* 1979; **60:** 520–30.

25 Holmgren A, Ovenfors CO. Heart volume at rest and during muscular work in the supine and in the sitting position. *Acta Med Scand* 1960; **167:** 267–77.

26 Kentala E, Heikkilä J, Pyörälä K. Variation of QRS amplitude in exercise ECG as an index of predicting result of physical training in patients with coronary heart disease. *Acta Med Scand* 1973; **194:** 81–6.

27 Lloyd-Thomas HG. The effect of exercise on the electrocardiogram in healthy subjects. *Br Heart J* 1961; **23:** 260–70.

28 Morris SN, Lovelace E, McHenry PL. Comparison of R wave and QRS amplitude during treadmill testing in normals and patients with coronary disease (abstract). *Am J Cardiol* 1979; **43:** 353.

29 Berman JL, Wynne J, Cohn PF. Hemodynamic correlates of increased R wave sum in multiple lead treadmill exercise tests (abstract). *Am J Cardiol* 1979; **43:** 354.

30 Battler A, Froelicher V, Slutsky R, Ashburn W. Relationship of QRS amplitude changes during exercise to left ventricular function and volumes and the diagnosis of coronary artery disease. *Circulation* 1979; **60:** 1004–13.

31 Wolthuis RA, Froelicher VF, Hopkirk A, Fischer JR, Keiser N. Normal electrocardiographic waveform characteristics during treadmill exercise testing. *Circulation* 1979; **60:** 1028–35.

32 Wagner S, Cohn K, Selzer A. Unreliability of exercise-induced R wave change as indexes of coronary artery disease. *Am J Cardiol* 1979; **44:** 1241–6.

33 Mann T, Brodie BR, Grossman W, McLaurin LP. Effect of angina on the left ventricular diastolic pressure-volume relationship. *Circulation* 1977; **55:** 761–6.

34 McCans JL, Parker JO. Left ventricular pressure-volume relationships during myocardial ischemia in man. *Circulation* 1973; **48:** 775–85.

35 Rerych SK, Scholz PM, Newman GE, Sabiston DC Jr, Jones RH. Cardiac function at rest and during exercise in normals and in patients with coronary heart disease: evaluation by radionuclide angiocardiography. *Ann Surg* 1978; **187:** 449–64.

36 Goldstein RE, Bennett ED, Leech GL. Effect of glyceryl trinitrate on echocardiographic left ventricular dimensions during exercise in the upright position. *Br Heart J* 1979; **42:** 245–54.

37 Rickards AF, Seabra-Gomes R. Observations on the effect of angina on the left ventricle, with special reference to diastolic behaviour. *Eur J Cardiol* 1978; **7,** suppl: 213–38.

38 Fox KM, Selwyn AP, Shillingford JP. Projection of electrocardiographic signs in praecordial maps after exercise in patients with ischaemic heart disease. *Br Heart J* 1979; **42:** 416–21.

39 Epstein SE. Limitations of electrocardiographic exercise testing. *N Engl J Med* 1979; **301:** 264–5.

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Br Heart J 1980; **44:** 518–23

Regional left ventricular wall motion from first-pass radionuclide angiocardiography using an Anger camera

Experimental and clinical study

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SUMMARY Experimental studies with a balloon phantom, and clinical studies were performed to evaluate first-pass radionuclide angiocardiography using a gamma camera in the assessment of regional wall motion.

The phantom studies showed that choice of isocount contour was not critical in edge detection. Adequate count densities could be achieved, but only at the expense of temporal resolution.

The clinical studies disclosed a good correlation with radiography in normal subjects and those with diffuse ventricular disease but a poor correlation in subjects with localised abnormalities of wall motion.

Radionuclide studies of the cardiac blood pools can be performed either during the first pass through the central circulation of a peripherally injected radionuclide bolus or when a blood pool tracer has come to equilibrium.

The first pass technique has several theoretical advantages over the equilibrium approach. The short data accumulation time (30 to 40 s) makes the method particularly suitable for the study of seriously ill subjects who may have difficulty lying still and for the demonstration of short-lived abnormalities. The good temporal separation between right and left heart phases of bolus transit means that the left ventricle can be studied in the right anterior oblique (RAO) view without interference from activity in the overlying right ventricle. Finally, background levels are low.

The major disadvantage of first-pass studies derives from the limited performance of conventional gamma cameras in dealing with high count rates. The resulting reduction in efficiency of detection of emitted radiation leads to the accumulation of left ventricular images from a relatively small number of scintillations (or counts), thereby compromising image resolution. Multicrystal cameras have been developed with better response to high count rates, but at the expense of spatial resolution and energy discrimination.

The purpose of this study was to determine how many counts per image were required for wall motion studies and to decide whether or not conventional gamma cameras were suitable. Both experimental studies using a balloon phantom and clinical studies were performed.

Methods

(a) PHANTOM STUDIES

The apparatus consisted of a fluid filled balloon suspended in a water bath at a depth of approximately 6 cm. ^{99}Tc^{m} as pertechnetate was added to the balloon which was imaged at volumes of 50 and 100 ml. A series of images was accumulated using a gamma camera and computer system. Each stored frame contained 1000 counts from the balloon and independent frames were summed to examine the effect of improving statistical accuracy. Background activity was varied by adding tracer to the water bath. An isocount contour technique was used to delineate the edge of the balloon image. Image dimensions were compared with actual dimensions from photographs.

(b) CLINICAL STUDIES

Forty-three subjects with a variety of cardiac disorders were studied by first-pass radionuclide angiocardiography. 15 mCi ^{99}Tc^{m} pertechnetate

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were injected intravenously as a bolus and the first pass of tracer through the central circulation was detected by a gamma camera placed in the 30° RAO position over the praecordium. Data were recorded in list mode and stored on magnetic disc. A left ventricular activity-time curve was used to identify individual cardiac cycles (intrinsic gating) during the left heart phase of bolus transit and each cycle was divided into eight equal time intervals. Data from corresponding intervals in successive cycles were summed to produce a series of images—a representative cine cycle. The 20 per cent isocount contour was arbitrarily chosen to represent the edge of the image. Movement of this contour was plotted as a third dimension against two axes representing (1) distance around the perimeter and (2) time from end-diastole to end-diastole. Values of equal displacement were joined to form a contour map.[1] The advantage of this form of presentation is that it is not necessary to identify the plane of the aortic valve which can be difficult in these images. Wall motion was considered in anterior, apical, and inferior ventricular regions and was classified as normal if there was inward displacement of two contour levels (1 cm) from the end-diastolic position. Movement inward of less than two contour levels, no movement, and outward systolic movement were classified as abnormal.

Each subject underwent radiographic ventriculography in the same view within two days. There were no significant changes of treatment between the two examinations. Again wall motion was considered in anterior, apical, and inferior regions and was classified as normal or abnormal by an experienced observer with no knowledge of the radionuclide results. The results were compared region by region with the radionuclide results.

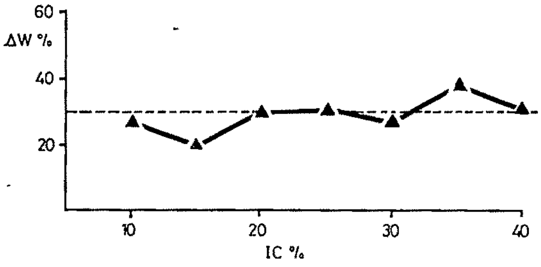

Fig. 1 *The effect of choice of isocount contour on the apparent change in width of the balloon phantom as it was emptied from 100 ml to 50 ml. W%, change in width as a percentage of 100 ml width; IC%, isocount contour as a percentage of peak counts; – – – – actual change (from photograph); —— apparent change.*

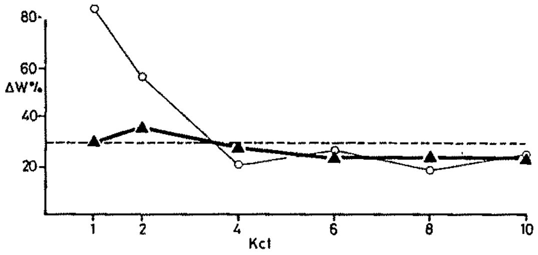

Fig. 2 *The effect of increasing count density on the apparent change in width of the balloon phantom as it was emptied from 100 ml to 50 ml. W%, change in width as a percentage of 100 ml width; Kct, kilo-counts per image for the 100 ml balloon; ▲, no added background; ○, background 40 per cent; – – – – actual change (from photograph)*

All studies were performed using a Radicamera Mk II with a standard, parallel hole collimator, and a Nuclear Data computer system.

Results

(a) PHANTOM STUDIES

The results are expressed in Fig. 1 and 2; those relating to width and area were similar; those relating to width have been chosen for illustration because this measurement has more relevance to wall motion studies and it avoids repetition. On emptying the balloon from 100 to 50 ml there was a 30 per cent decrease in maximum width. Fig. 1 illustrates the effect of taking different isocount contours to represent the image edge. Though the choice of isocount contour affected the apparent absolute size of the balloon, the estimate of change in size was independent of isocount contour between 10 and 40 per cent.

Fig. 2 illustrates the effect of varying image counts at two different background levels. With background up to 40 per cent it is possible to obtain reliable estimates of change in width provided that 4000 counts are accumulated in the region of interest.

(b) CLINICAL STUDIES

Fig. 3 shows an 8 frame cine cycle and Fig. 4 a contour map. The number of counts in each ventricular image varied between 1000 and 4000 at end-diastole. Background levels varied between 15 and 35 per cent of peak intraventricular activity.

Table 1 shows that in the group as a whole there was a good correlation between radiographic and radionuclide angiocardiography. Twenty-three subjects had radiographically normal ventricles. In

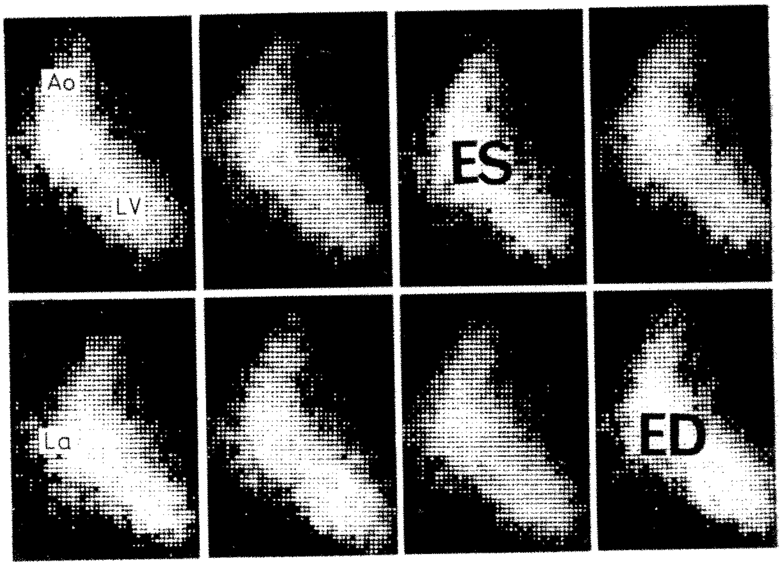

Fig. 3 *Representative cine cycle. ED, end-diastole; ES, end-systole; LV, left ventricle; LA, left atrium; Ao, aorta.*

these subjects 68 out of 75 regions were normal on the radionuclide study. Ten subjects had diffusely abnormal ventricles and in these the nuclear technique showed abnormalities in 25 out of 30 regions. Results were less good in those with localised wall motion abnormalities as shown in Table 2.

Discussion

The number of counts in each image depends upon count rate, data collection time, and temporal resolution. Therefore, in equilibrium studies it is most easily increased by prolonging data collection time. In first-pass studies, which have a finite interval for data collection, it can be done by improving detection efficiency (multicrystal cameras) or by decreasing temporal resolution.

Using equilibrium studies, Zaret *et al.*[2] accumulated 300 000 counts in each total end-diastolic image, and Rigo *et al.*,[3] 200 000 counts, collecting data from 200 to 400 cardiac cycles. Improving temporal resolution by producing 80 to 100 frame representative cine cycles[4] necessitated data summation from 1200 to 1500 cycles. Some groups have attempted to reduce data collection time and the risk of motion artefact. Sneed *et al.*[5] accumulated 150 000 counts over four minutes with a temporal resolution of nine frames for each representative cycle. Bacharach *et al.*[6] argue that no advantage is gained by imaging for 10 rather than two and a half minutes. This group has used the short data collection time to study transient, exercise, and drug induced changes.[7–10] The figures quoted above refer to the total counts in an end-diastolic frame. This is not the same as intraventricular counts. Maddox *et al.*[11] estimated that out of 300 000 counts in an end-diastolic frame only 30 000 came from the ventricle. Burrow *et al.*[12] calculate 18 500 counts from the left ventricle after background correction.

Using a multicrystal camera for first-pass studies, Schad[13] found 30 000 counts in the uncorrected end-diastolic frame of which 3000 to 13 000 (mean 9600) actually came from the ventricle. This was with a time resolution of 50 ms. Marshall *et al.*[14 15] using similar equipment but sampling from fewer cardiac cycles, achieved 3300 ± 2000 counts for the ventricular image. Again using similar equipment, Bodenheimer *et al.*[16] could obtain 3723 to 10 268 (mean 6221) counts for each ventricular image after background subtraction.

First-pass wall motion studies have also been performed with single crystal cameras. Kostuk *et al.*[17] and Jengo *et al.*[18] do not quote count densities. Pachinger *et al.*[19] quote 14 000 to 17 000 counts for the total field in the right ventricular phase of bolus transit. Peak activity in the left heart phase and counts for each image are not quoted. Hecht *et al.*[20] claim 79 counts in the ventricle from the end-diastolic frame and sum 10 to 12 such frames producing approximately 800 to 1000 counts for the ventricle in the representative cine cycle. They believe that objective methods of edge detection may compensate for the relatively low count density.

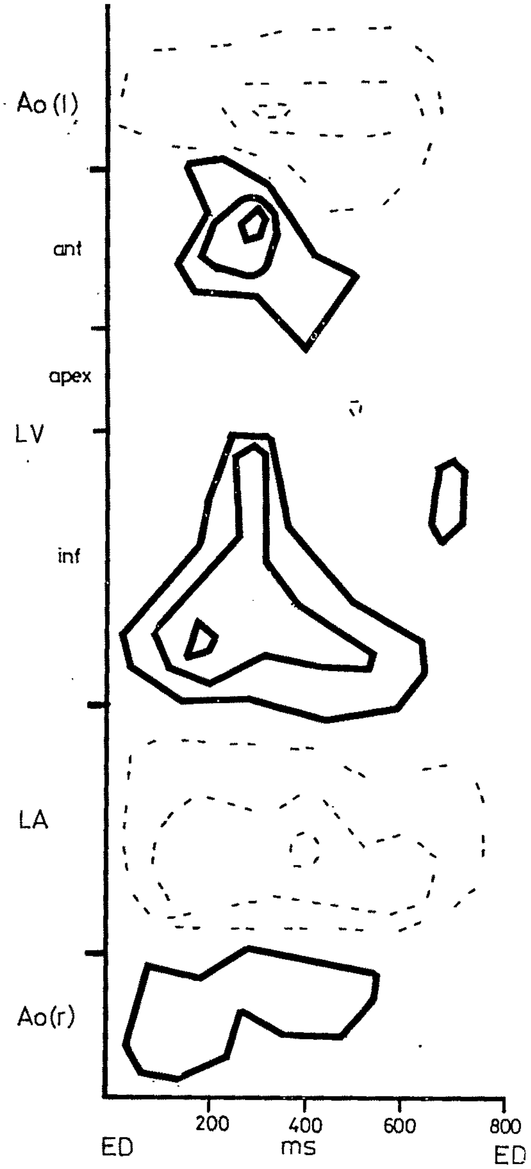

Fig. 4 *Contour map representation of wall motion. The vertical axis corresponds to position along the perimeter of the left ventricle, left atrium, and aorta. The horizontal axis represents time into the cardiac cycle. Each solid contour represents a movement inwards of 5 mm from the end-diastolic position and each broken contour a movement of 5 mm outwards. Ao(1), left side of aortic root; Ao(r), right side of aortic root; LV, left ventricle; LA, left atrium; ED, end-diastole. Note inward movement of proximal anterior and inferior left ventricular walls with apical and distal anterior akinesis. Left atrium expands. Both walls of aorta move to the left but the left wall to a greater extent than the right. This represents movement of the aorta as a whole plus apparent systolic aortic expansion.*

Table 1 *Comparison of radiographic and radionuclide assessment of regional wall motion in 43 subjects (three regions per subject)*

Radionuclide imaging	*Radiography*	
	Normal	*Abnormal*
Normal	76	10
Abnormal	11	32

The admittedly simplified phantom studies suggest that, at background levels comparable to clinical studies, 4000 counts for the end-diastolic image should give a reasonable estimate of wall motion with an ejection fraction of 50 per cent. Fewer counts than this may give correct estimates under more favourable background levels or if ejection is less. As the counts per 100 ml balloon fall below 2000 there is a progressive tendency to overestimate the percentage decrease in width. This effect is produced by a progressive underestimation of the size of the 50 ml balloon in the presence of added background activity.

It was apparent that to achieve desired count density using this equipment a time resolution of eight frames per representative cycle was the maximum that could be achieved. Even then the figures are barely adequate. The limited temporal resolution is of less importance at end-diastole because of the relatively prolonged maintenance of the end-diastolic position, but it may well underestimate the maximum extent of systolic inward movement. The phantom studies also showed that choice of isocount contour for edge definition has little effect on results (Fig. 1).

It is not unreasonable to expect that future developments in instrumentation may lead to a fivefold increase in maximum count rate; this should be a major benefit to first-pass studies.

Radiographic cineangiography is the accepted standard by which other techniques for the evaluation of wall motion are assessed. Certain factors would, however, lead us to expect a less than complete agreement between radionuclide and

Table 2 *Comparison of radiographic and radionuclide assessment of regional wall motion: eight subjects with localised abnormalities of wall motion by radiography (three regions per subject)*

Radionuclide imaging	*Radiography*	
	Normal	*Abnormal*
Normal	8	5
Abnormal	4	7

radiographic studies. Cardiac catheterisation is carried out on subjects who may be sedated and a considerable amount of emotional stress is involved. By the time ventriculography is performed the patient has been lying flat for some time. The injection of contrast material into the ventricle under pressure can affect wall motion, though perhaps not over the first five beats.[21] In addition the two studies may not be directly comparable. Radiography provides strictly two-dimensional information whereas the radionuclide approach probably provides three-dimensional estimates of regional function. Finally, no correction is made in the radionuclide studies for movement of the heart as a whole whereas this is probably done automatically with subjective reporting of radiographic angiograms.

Table 1 shows a reasonable overall agreement between the two techniques. The results show a closer correlation in radiographically normal and diffusely abnormal ventricles (Tables 1 and 2) than in subjects with localised disease. In diffusely abnormal ventricles there is prolonged bolus transit which gives a greater opportunity for data collection. The ventricle is dilated and therefore end-diastolic counts are higher, as are end-systolic counts because of the reduced ejection fraction. In normal ventricles the end-diastolic counts are less and the good ejection fraction means low end-systolic counts. This should serve only to accentuate the normal appearance. In ventricles with good ejection despite localised wall motion disorders any underestimation of end-systolic dimension would tend to obscure the abnormality. In addition the spatial resolution may not be adequate to detect small areas of abnormality, especially when combined with limited temporal resolution.

Conclusion

First-pass wall motion studies place severe demands on conventional gamma cameras. In this study wall motion analysis was reasonably reliable in normal subjects and subjects with diffuse ventricular disease but not in subjects with more localised disorders of wall motion. Improved results can be expected with more sophisticated equipment.

This work was supported by the British Heart Foundation.

References

1 Gibson DG, Prewitt TA, Brown DJ. Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. *Br Heart J* 1975; **38:** 1010–19.

2 Zaret BL, Strauss HW, Hurley PJ, Natarajan TK, Pitt B. A noninvasive scintiphotographic method for detecting regional ventricular dysfunction in man. *N Engl J Med* 1971; **284:** 1165–70.

3 Rigo P, Murray M, Strauss HW, Pitt B. Scintiphotographic evaluation of patients with suspected left ventricular aneurysm. *Circulation* 1974; **50:** 985–91.

4 Green MV, Ostrow HG, Douglas MA, *et al.* High temporal resolution ECG-gated scintigraphic angiocardiography. *J Nucl Med* 1975; **16:** 95–8.

5 Sneed A, Mishkin FS, Kaushik VS, Reese I. Radionuclide cinecardiography using minicomputer generated sequential gated images. *Br Heart J* 1977; **39:** 982–7.

6 Bacharach SL, Green MV, Borer JS, Douglas MA, Ostrow HG, Johnston GS. A real-time system for multi-image gated cardiac studies. *J Nucl Med* 1977; **18:** 79–84.

7 Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS. Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest during exercise in patients with coronary-artery disease. *N Engl J Med* 1977; **296:** 839–44.

8 Borer JS, Bacharach SL, Green MV, Kent KM, Johnston GS, Epstein SE, Effect of nitroglycerine on exercise-induced abnormalities of left ventricular regional function and ejection fraction in coronary artery disease. *Circulation* 1978; **57:** 314–20.

9 Bodenheimer MM, Banka VS, Fooshee CM, Gillespie JA, Helfant RH. Detection of coronary heart disease using radionuclide determined regional ejection fraction at rest and during hand grip exercise: correlation with coronary arteriography. *Circulation* 1978; **58:** 640–8.

10 Marshall RC, Berger HJ, Reduto LA, Cohen LS, Gottschalk A, Zaret BL. Assessment of cardiac performance with quantitative radionuclide angiocardiography: effects of oral propranolol on global and regional left ventricular function in coronary artery disease. *Circulation* 1978; **58:** 808–14.

11 Maddox DE, Holman BL, Wynne J, *et al.* Ejection fraction image: a noninvasive index of regional left ventricular wall motion. *Am J Cardiol* 1978; **41:** 1230–87.

12 Burow RD, Strauss HW, Singleton R, *et al.* Analysis of left ventricular function from multiple gated acquisition cardiac blood pool imaging. *Circulation* 1977; **56:** 1024–8.

13 Schad N. Nontraumatic assessment of left ventricular wall motion and regional stroke volume after myocardial infarction. *J Nucl Med* 1977; **18:** 333–41.

14 Marshall RC, Berger HS, Costin JC, *et al.* Assessment of cardiac performance with quantitative radionuclide angiocardiography: sequential left ventricular ejection fraction, normalised left ventricular ejection rate, and regional wall motion. *Circulation* 1977; **56:** 820–9.

15 Marshall RC, Berger HJ, Reduto LA, Gottschalk A,

Zaret BL. Variability in sequential measures of left ventricular performance assessed with radionuclide angiocardiography. *Am J Cardiol* 1978; **41:** 531–6.

16 Bodenheimer MM, Banka VS, Fooshee CM, Hermann GA, Helfant RH. Quantitative radionuclide angiography in the right anterior oblique view: comparison with contrast ventriculography. *Am J Cardiol* 1978; **41:** 718–25.

17 Kostuk WJ, Ehsani AA, Karliner JS, *et al.* Left ventricular performance after myocardial infarction assessed by radioisotope angiocardiography. *Circulation* 1973; **47:** 242–9.

18 Jengo JA, Mena I, Blaufuss A, Criley JM. Evaluation of left ventricular function (ejection fraction and segmental wall motion) by single pass radioisotope angiography. *Circulation* 1978; **57:** 326–32.

19 Pachinger O, Ogris E, Probst P, Joskowics G, Sochor H, Kaindl F. Assessment of left ventricular performance and myocardial viability using quantitative radioisotope techniques. *Br Heart J* 1979; **42:** 205–13.

20 Hecht HS, Mirell SG, Rolett EL, Blahd WH. Left-ventricular ejection fraction and segmental wall motion by peripheral first pass radionuclide angiography. *J Nucl Med* 1978; **19:** 17–23.

21 Karliner JS, Bouchard RJ, Gault JH. Haemodynamic effects of angiographic contrast material in man: a beat-by-beat analysis. *Br Heart J* 1972; **34:** 347–55.

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Br Heart J 1980; **44:** 524–8

New intervention in mitral valve prolapse
Use of cold pressor test during echocardiography

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SUMMARY A study was performed in 13 patients with idiopathic mitral valve prolapse and in 21 control subjects to assess the effect of the cold pressor test on systolic motion of the mitral valve. A significant increase in blood pressure occurred in 10 patients with mitral valve prolapse and in 19 controls after immersion of one hand in ice-cold water. M-mode echocardiographic recordings from the mitral valve were obtained in all patients before, during, and after the cold pressor test, together with simultaneous phonocardiograms in selected patients. Nine out of 10 patients with mitral valve prolapse and a hypertensive response to the cold stimulus showed a significant increase in the depth of mitral valve prolapse during the cold pressor test whereas in three patients with mitral valve prolapse and no hypertensive response the depth of mitral valve prolapse did not change during cold stimulation. Three patients with previously demonstrated mitral valve prolapse had equivocal resting echocardiograms but developed diagnostic evidence of mitral valve prolapse during the cold pressor test. No evidence of mitral valve prolapse was seen in any of the control subjects before, during, or after the cold pressor test.

In four patients with mitral valve prolapse and a hypertensive response to cold stimulation the systolic click was delayed by the cold pressor test, whereas the time of the systolic click remained constant in the three patients whose blood pressure did not increase.

It is concluded that the cold pressor test provides a stimulus sufficient to delay the onset and increase the depth of mitral valve prolapse, thereby enhancing the diagnostic sensitivity of echocardiography in this condition.

Echocardiography is the most important technique for the non-invasive diagnosis of mitral valve prolapse. Despite careful echocardiographic examination at rest, however, some patients with mitral valve prolapse have normal or non-diagnostic mitral echograms. In some patients this may be a result of localised prolapse occurring in a part of the mitral valve inaccessible to the ultrasound beam. In other patients shallow prolapse of the mitral valve at the time of the examination may fail to give rise to diagnostic echocardiographic abnormalities. In the latter situation particularly, certain physiological and pharmacological interventions may increase the diagnostic sensitivity of echocardiography. Such manoeuvres as head-up tilt, Valsalva, and amyl nitrite inhalation exaggerate the echocardiographic features of mitral valve prolapse and alter the timing of its onset,[1 2] but these manoeuvres may produce the echocardiographic appearances of mitral valve prolapse in normal people.[3]

The cold pressor test[4] has not previously been described as a diagnostic intervention in patients with mitral valve prolapse. In the present study we examined the effect of this stimulus on the echocardiographic and phonocardiographic findings in patients with mitral valve prolapse and in a group of control subjects.

Patients and methods

Thirteen patients with idiopathic mitral valve prolapse and 21 control subjects were studied. Details of the patients with mitral valve prolapse are shown in the Table. All had clinical signs suggesting mitral valve prolapse which had been confirmed previously by echocardiography in all cases. Four patients had selective coronary arterio-

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Table *Clinical details of patients with mitral valve prolapse*

Case no.	*Sex*	*Age (y)*	*Symptoms*	*Signs*	*Resting electrocardiogram*
1	M	22	Palpitation, syncope	ESC, soft ESM	Normal
2	F	49	Dyspnoea, palpitation	MSC, LSM	Normal
3*	M	55	Chest pain, previous cardiac arrest	ESC	T waves flat to inverted in inferior and lateral leads
4*	F	49	Chest pain	MSC	T wave flat or inverted inferior and anterior leads
5	F	51	Dyspnoea, palpitation	MSC, LSM	ST sagging and T waves flat or inverted inferolaterally
6	F	48	Dyspnoea, palpitation	MSC	Normal
7	F	30	Intermittent awareness of murmur	MSC, intermittent LSM	Normal
8	F	40	Atypical chest pain, fatigue, dyspnoea, palpitation	MSC	T wave flat or inverted inferior and lateral leads
9	F	32	Chest pain, fatigue, palpitation	MSC, LSM	T wave flat or inverted inferior and lateral leads; frequent VPBs
10*	F	58	Atypical chest pain, fatigue, dyspnoea, palpitation	MSC, LSM	Sagging ST segment inferior leads; occasional VPBs
11	M	11	Nil	LSM	Normal
12*	M	34	Atypical chest pain, dyspnoea	MSC, LSM	Sagging ST segment inferior leads
13	M	52	Atypical chest pain	MSC, LSM	Normal

ESC, early systolic click; ESM, ejection systolic murmur; MSC, mid-systolic click; LSM, late-systolic murmur; VPB, ventricular premature beat. * Coronary arteriography performed (normal).

graphy which was normal and contrast left ventriculography which further confirmed mitral valve prolapse. Cardiac catheterisation was not performed in the remainder, in whom coronary artery disease was not suspected clinically. The control group comprised six patients with angiographically proven coronary artery disease, two patients with non-obstructive hypertrophic cardiomyopathy, and 13 normal subjects.

All patients were studied while resting on a couch in the 30° left oblique position. Using a Dinamap automatic sphygmomanometer, readings of heart rate and blood pressure were obtained at one-minute intervals throughout the study, and were recorded by an independent observer. M-mode echocardiograms were recorded from the mitral valve at the same intervals, using an Ekoline 20A ultrasonoscope with a 2·25 MHz transducer focused at 10 cm and maintained in a constant position by hand. The transducer was initially aligned so as to show the maximum possible depth of mitral valve prolapse in each patient. Simultaneous phonocardiograms were recorded in seven patients. All recordings were made during a three-minute pretest period, during five minutes with the patient's hand immersed in ice-cold water, and for three minutes afterwards.

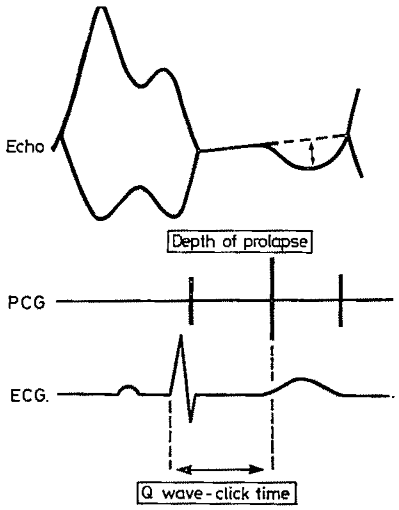

Fig. 1 *The measured depth of mitral valve prolapse* (small arrow) *is shown on a diagrammatic echocardiogram, with phonocardiogram (PCG) and electrocardiogram (ECG) illustrating the Q wave—systolic click time* (large arrow).

The echocardiograms were analysed without knowledge of the timing of a given recording or of the blood pressure response in each patient. The depth of mitral valve prolapse was measured from the echocardiograms as the maximum depth of posterior displacement of the mitral echo during systole (Fig. 1). On each recording the depth of mitral valve prolapse was taken as the average of measurements made over five consecutive cardiac cycles, thus minimising the effect of respiratory movement. Where phonocardiograms were obtained the time from the initial QRS deflection on the electrocardiogram to the systolic click on the phonocardiogram (Q wave—click time) was also measured and averaged over five consecutive cycles.

Analysis of variance was used to assess the statistical significance of the results. The null hypothesis was rejected when its probability was less than 0·05.

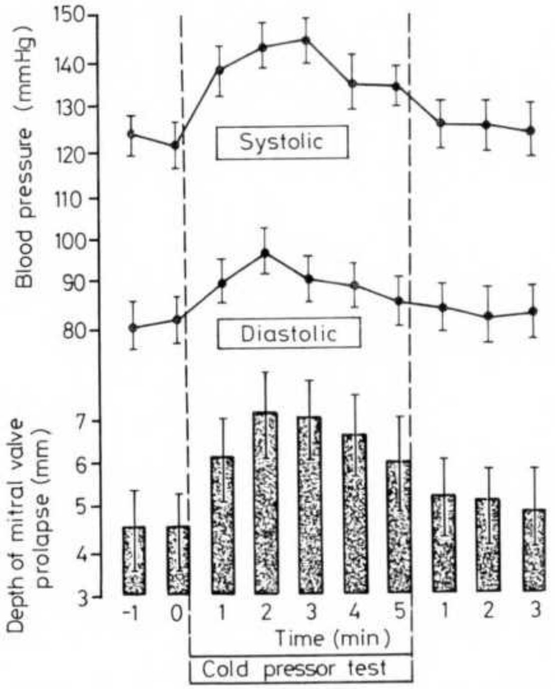

Fig. 2 *Mean systolic and diastolic blood pressures (SE) and mean depth of mitral valve prolapse in 10 patients with mitral valve prolapse who showed a pressor response to cold.*

Results

Ten out of 13 patients with mitral valve prolapse showed a hypertensive response to the cold stimulus (Fig. 2) and during cold stimulation nine of these developed a significant increase in the depth of prolapse ($p < 0 \cdot 001$), which had returned to resting or near-resting levels three minutes after removal of the cold stimulus (Fig. 2 and 3). Furthermore, in three patients with previously documented mitral valve prolapse the resting echocardiograms on the day of the study were equivocal. During the cold pressor test abrupt posterior motion of the mitral echo in mid-systole, diagnostic of mitral valve prolapse, was seen in these three patients. In contrast, three patients with mitral valve prolapse had no hypertensive response to cold, and no significant change in the depth of mitral valve prolapse occurred during the study. In the control group 19 had a hypertensive response but none showed evidence of mitral valve prolapse before, during, or after the cold pressor test. In two control subjects no hypertensive response was observed and the mitral echograms remained normal.

Phonocardiograms were obtained from four patients with mitral valve prolapse who experienced a pressor response to cold stimulation. In all four there was a transient increase in Q wave—click time of 30 to 50 ms (mean 35 ms) during the cold pressor test (Fig. 4) and the intensity of the late systolic murmur increased in one patient. In the three patients with mitral valve prolapse who had phonocardiograms recorded but who showed no hypertensive response the Q wave—click time remained constant.

In 11 patients with mitral valve prolapse the heart rate increased during cold stimulation. Ten had increases of one to eight beats per minute and one patient had an increase of 18 beats per minute. Increases in heart rate tended to precede the in-

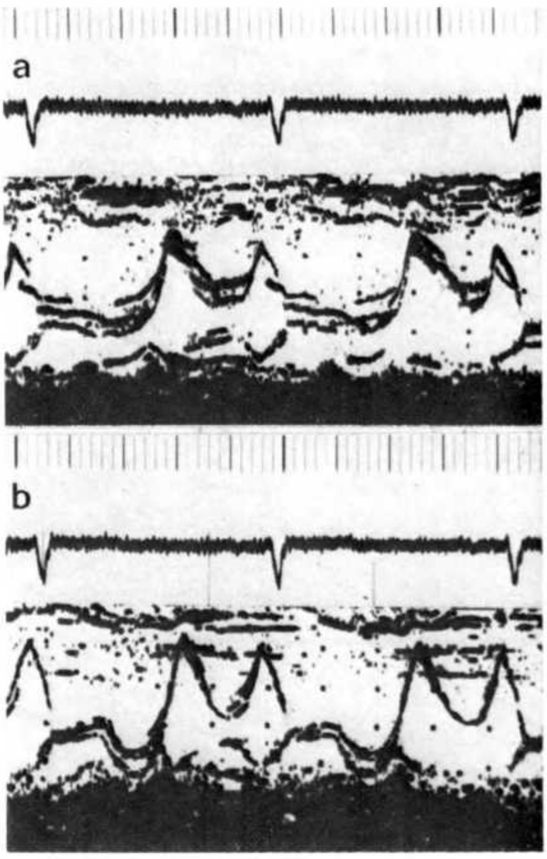

Fig. 3 *Mitral echograms from a patient with mitral valve prolapse:* (a) *before the cold pressor test showing pansystolic posterior sagging of the dominant echoes from the mitral valve and* (b) *during the cold pressor test showing severe mid-systolic buckling of the mitral echo.*

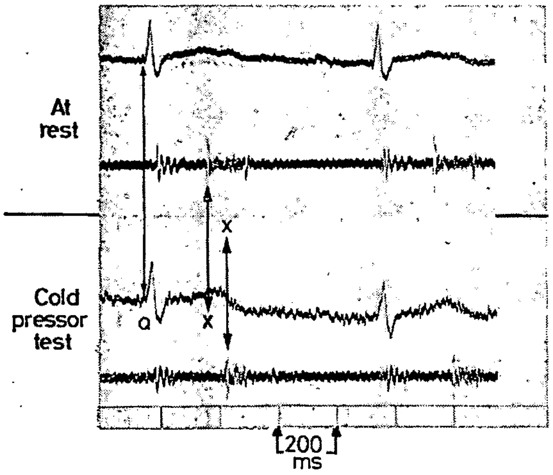

Fig. 4 *Simultaneous electrocardiograms and phonocardiograms from a patient with mitral valve prolapse. In the upper trace, recorded at rest, the QRS complex has been aligned with that of the lower trace, recorded during cold pressor test. The delay in the systolic click caused by the cold pressor test is indicated by the two arrows* (X).

creases in blood pressure: the magnitude of the heart rate increase showed no relation to the magnitude of the pressor response or the increase in depth of prolapse. Two patients showed a pressor response with increased depth of mitral valve prolapse in the presence of a slight fall in heart rate during cold stimulation.

Discussion

Patients with mitral valve prolapse may be asymptomatic but many present with symptoms such as chest pain, dyspnoea, palpitation, or syncope, usually out of proportion to any measurable haemodynamic abnormality. The characteristic clinical signs of a systolic click, with or without a late systolic murmur, may suggest the diagnosis. Some patients, however, have no abnormal physical signs.[5] In this situation echocardiography is the only non-invasive means of diagnosing mitral valve prolapse, but even the echocardiographic signs may be intermittent or equivocal. While abrupt posterior motion of the mitral valve echo in mid-systole is specific for mitral valve prolapse the distinction between holosystolic mitral valve prolapse and non-specific systolic sagging of the mitral echo is less obvious. Physiological and pharmacological manoeuvres may be used to alter the timing of onset of the mitral valve prolapse seen on the echocardiogram and of the closely related systolic click.[1 2] Mathey *et al.*[2] have shown that the onset of mitral valve prolapse occurs at a relatively fixed ventricular dimension in individual patients. Thus, a delay in onset of the mitral valve prolapse, as seen in our patients during the cold pressor test, may be explained either by an increase in left ventricular end-diastolic dimension or by a reduction in left ventricular performance before the onset of prolapse. In either situation the left ventricle would take longer to reach the critical dimension at which prolapse occurs. Our results do not, however, distinguish between these two mechanisms, as left ventricular dimensions were not measured in this study focusing as it did primarily on mitral valve motion.

In our patients the depth of mitral valve prolapse was increased during the cold pressor test. Devereux *et al.*[6] suggest that manoeuvres that reduce left ventricular cavity size cause mitral valve prolapse to be both earlier and greater and that those that increase left ventricular cavity size result in later and lesser prolapse. But mitral valve prolapse was both later and greater during the cold pressor test, an intervention that increases blood pressure and that would not be expected to reduce left ventricular volume in the absence of consistent increases in heart rate. This suggests that the depth of mitral valve prolapse is not entirely dependent on left ventricular dimensions, and our results showed a relation between increases in blood pressure and depth of mitral valve prolapse. Further evidence that the depth of mitral valve prolapse is not determined solely by left ventricular dimensions may be obtained by examining the motion of the mitral valve echo in mitral valve prolapse. The depth of prolapse begins to decrease immediately after the aortic component of the second heart sound (aortic valve closure), as left ventricular pressure falls during isovolumic relaxation (D W Pitcher, unpublished observations). It therefore seems probable that while the onset of mitral valve prolapse is determined by left ventricular dimensions, the depth of prolapse is determined, at least in part, by left ventricular systolic pressure.

Like other manoeuvres causing deeper mitral valve prolapse, the cold pressor test increases the sensitivity of echocardiographic detection of prolapse. However, Valsalva, head-up tilting, or amyl nitrite inhalation cause earlier as well as deeper prolapse. These manoeuvres may convert the specific echo pattern of mid-systolic prolapse to the less specific holosystolic prolapse, and may also produce echocardiographic appearances of mitral valve prolapse in normal people.[3] No such abnormalities were caused by the cold pressor test in our control group. By causing later as well as deeper prolapse, the cold pressor test will tend to convert a non-specific echogram showing holosystolic sagging of the mitral echo to the specific pattern of mid-systolic mitral valve prolapse and may thereby enhance the sensitivity of echocardiography in mitral valve prolapse without loss of specificity.

As a result of these studies we feel that the cold pressor test is indicated during echocardiography in patients presenting with unexplained chest pain, arrhythmias, or isolated late-systolic murmurs, in whom the echocardiogram is normal or equivocal at rest. Detection of otherwise "silent" mitral valve prolapse in this way may prevent needless further investigation. Further studies in such patients are indicated to assess the sensitivity of the cold pressor test in provoking echocardiographic evidence of mitral valve prolapse when the resting echocardiogram fails to detect it.

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References

1 Winkle RA, Goodman DJ, Popp RL. Simultaneous echocardiographic-phonocardiographic recordings at rest and during amyl nitrite administration in patients with mitral valve prolapse. *Circulation* 1975; **51:** 522–9.
2 Mathey DG, Decoodt PR, Allen HN, Swan HJC. The determinants of onset of mitral valve prolapse in the systolic click-late systolic murmur syndrome. *Circulation* 1976; **53:** 872–8.
3 Roye JA, Basta LL. Echocardiographic pattern of mitral valve prolapse produced with special maneuvers in healthy individuals (abstract). *Circulation* 1975; **52,** suppl II: 235.
4 Greene MA, Boltax AJ, Lustig GA, Rogow E. Circulatory dynamics during the cold pressor test. *Am J Cardiol* 1965; **16:** 54–60.
5 Jeresaty RM. *Mitral valve prolapse.* New York: Raven, 1979: 53–60.
6 Devereux RB, Perloff JK, Reichek N, Josephson ME. Mitral valve prolapse. *Circulation* 1976; **54:** 3–14.

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Atrioventricular nodal function in progressive systemic sclerosis: electrophysiological and morphological findings

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SUMMARY Electrophysiological data consistent with atrioventricular nodal dysfunction were obtained in 10 out of 19 patients with progressive systemic sclerosis (scleroderma). Conducting system studies were carried out in a further seven patients with progressive systemic sclerosis. In each the proximal portion of the atrioventricular node was consistently found to be smaller and more slender. It is postulated that there is a relation between proximal atrioventricular nodal structural alterations and impaired atrioventricular nodal function.

Conducting system disorders are found in progressive systemic sclerosis.[1–3] First degree atrioventricular block occurred in as many as 20 per cent of patients in one of these series[2] and in all three series there was at least one case with complete atrioventricular block. In an additional case of progressive systemic sclerosis with complete heart block, at necropsy the atrioventricular node was found to be fused with the central fibrous body of the heart. At the bifurcation of the bundle there was an acute degenerative change and there was fibrosis of the right bundle.[4] In a necropsy study of eight further patients James[5] observed that before death at least five of them had had significant conducting system disease localised at the atrioventricular node or bundle of His, as judged by the electrocardiogram, and that in each there were severe morphological abnormalities present at these sites and at the sinus node. He felt that the normal difference in collagen content between the sinus node on the one hand and the atrioventricular node junctional tissues on the other may partially explain why fibrosis was so much more conspicuous in the former. He concluded that a combination of sinus node destruction and excess focal fibrotic partitioning in the atrioventricular junction was the likely basis for a high frequency of paroxysmal supraventricular tachycardia, the electrophysiological consequences being failure of normal automaticity together with the availability of multiple anatomical routes for atrioventricular junctional re-entry. Though the series of Ridolfi and colleagues[6] contained three patients with first degree heart block and one with complete block on the electrocardiogram, at necropsy no significant atrioventricular nodal disease was found. Recently, however, in a necropsy specimen of the atrioventricular node in a patient with progressive systemic sclerosis, we found that there was loss of tissue at the proximal end of the structure. Because of the discrepancy of the findings in the published reports, the present study was undertaken to confirm this morphological observation of ours and to examine atrioventricular nodal function to see how reliable the electrocardiogram was in identifying atrioventricular nodal disease.

Subjects and methods

The last seven patients who died at the ULCA Medical Center with the diagnosis of progressive systemic sclerosis were studied. After a routine necropsy, the conducting system, including the atrioventricular node, atrioventricular bundle, and bundle-branches were removed in a single block. The blocks were processed in the manner previously described.[7] This, in brief, involved sectioning at 5 μ intervals and retention of every fifth section. These sections were made longitudinally parallel to the atrioventricular node and bundle and mounted three to a slide. Alternate slides were stained with haematoxylin, phloxine, and tartrazine.

By sectioning the atrioventricular node and bundle in a direction longitudinally parallel rather than at right angles to the conducting tissue,

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complete sectioning of the structures was achieved in fewer sections than in the traditional method.[8] This enabled us to compare more similar sections by relating them to the distance from the right atrial endocardium than other more arbitrary methods.

For the electrophysiological studies of atrioventricular nodal function 19 patients with progressive systemic sclerosis being followed in the Division of Rheumatology at UCLA were prospectively studied by a right heart catheterisation between August 1977 and January 1979. Eighteen of the patients met the criteria of the American Rheumatism Association[9] for scleroderma and one patient had the syndrome of calcinosis, Raynard's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia.[10] The mean age of the patients was 52 years and the average duration of the disease was 12 years. The procedure for the studies was approved by the UCLA Human Subject Protection Committee and fully informed consent was obtained from all the subjects.

The PR interval was obtained from the surface leads and the atrioventricular nodal conduction time (AH interval) was measured during the same cardiac cycles. Right atrial pacing was performed until second degree heart block occurred. The effective and functional refractory periods were measured by pacing the atrium at a standard cycle length of 590–620 ms and applying an extra stimulus every eighth complex. Patients in whom no response was provoked had refractory period measurements made by applying an extra stimulus after every eighth spontaneous beat (cases 4, 11, 12). One patient had a sinus tachycardia and was paced with a cycle length of 500 ms (case 16) and in case 17 refractory period measurements were not obtained at the standard cycle length but were obtained at a paced cycle length of 680 ms.

Results

CLINICAL AND ELECTROPHYSIOLOGICAL FINDINGS

In five of the seven patients who died electrocardiograms immediately before death showed no specific conduction system disorder. One patient had complete atrioventricular block and the last a prolonged PR interval.

Electrocardiographic and electrophysiological data relating to atrioventricular function in the 19 patients are listed in Table 1. Two patients had prolonged PR intervals and prolonged atrioventricular nodal (AH) conduction times (cases 12, 19). A further patient (case 10) had a prolonged atrioventricular nodal conduction time which was not reflected in a prolonged PR interval. Two patients had atrioventricular nodal conduction times of 70 ms or less (cases 2, 17) and a further two (cases 1, 16) had conduction times close to this. The refractory period measurements of the atrioventricular node disclosed that eight patients had abnormally prolonged intervals (cases 4, 11, 12, 14, 15, 16, 18, 19). The response of atrioventricular nodal conduction to atrial pacing is illustrated in Fig. 1. Cases 12 and 19 showed a rather straight incremental change in atrioventricular nodal conduction, unlike the more usual exponential increase in conduction time with decrease in cycle length. Cases 16 and 17 had a relatively slight incremental change in atrioventricular nodal conduction from the longer cycle lengths of 500 to 300 ms in case 16 and from 675 to 375 in case 17. The other measurements of cycle length in these cases were around 300 ms with AH intervals of between 100 and 120 ms.

While it is quite possible that these data are incomplete it is possible that at the shorter cycle lengths conduction was down pathways with a

Table 1 *Measurements of atrioventricular nodal function (ms)*

Case no.	*Cycle length (ms)*	*PR interval*	*AH interval*	*Paced cycle length*	*AV node*	
					ERP	*FRP*
1	780	150	75	600	280	350
2	680	160	70	600	320	360
3	833	165	100	590	340	350
4	833	175	115	600 and 850*	300*	360*
5	706	190	105	610	320	360
6	840	180	110	590	220	300
7	857	200	115	590	320	350
8	857	175	115	600	350	370
9	706	155	90	600	230	340
10	760	185	135	600	240	300
11	720	190	90	600 and 740*	410*	740*
12	1000	235	180	600 and 930*	440*	940*
13	840	180	90	610	380	390
14	667	155	85	600	240	540
15	833	160	80	600	300	540
16	600	135	75	— 500†	—	—
17	800	150	65	600	280	340
18	800	180	110	620	340	520
19	680	220	125	600 and 680‡	340†	540†
Normal		⩽200	⩽120	600	⩽400	⩽500

* Spontaneous cycle length and refractory period measurements (at the paced cycle lengths the atrioventricular node was entirely refractory).

† Longer cycle length at which overdrive of sinus tachycardia was possible.

‡ Second paced cycle length.

ERP, effective refractory period. FRP, functional refractory period.

longer conduction time but shorter refractory periods.

MORPHOLOGICAL FINDINGS

The seven patients in whom the heart was available for study all had had progressive systemic sclerosis with involvement of the lungs, skin, and gastrointestinal tract for a number of years. Table 2 lists the cardiac lesions found in these patients.

In the conducting system, the atrioventricular nodes were remarkably similar in all seven cases. Instead of the normal appearance of a rather pear-shaped proximal atrioventricular node (Fig. 2a) the proximal part of the node was slender and nearly the same diameter as the distal part (Fig. 2b). The nodal structure did contain more fibrous tissue in the patients who had progressive systemic sclerosis, but this was only apparent, however, when age-matched controls were studied. In one case (Fig. 3) there clearly was discontinuity between the proximal portion of the atrioventricular node, and the distal portion and atrioventricular bundle.

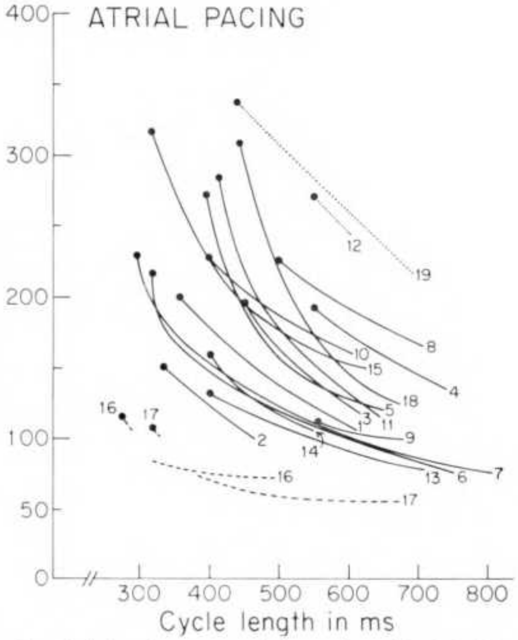

Fig. 1 *Atrial pacing to second degree heart block in 19 patients with progressive systemic sclerosis. The cycle length (ms) is plotted against the atrioventricular conduction (A–H). Cases 12 and 19 have a long conducting interval and straight curve. Cases 2, 16, and 17 have abnormal curves, the latter two with broken curves which are consistent with dual atrioventricular nodal pathways.*

Table 2 *Cardiac involvement in progressive systemic sclerosis*

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*	*Case 7*
Pericardial effusion	+	+	+	+	+	+	+
Intimal proliferation of the arteries	+	+	+	+	+	+	+
Scleroderma cardiomyopathy		+					
Area of focal necrosis							+
Right ventricular hypertrophy			+	+	+		
Atrioventricular node abnormalities	+	+	+	+	+	+	+

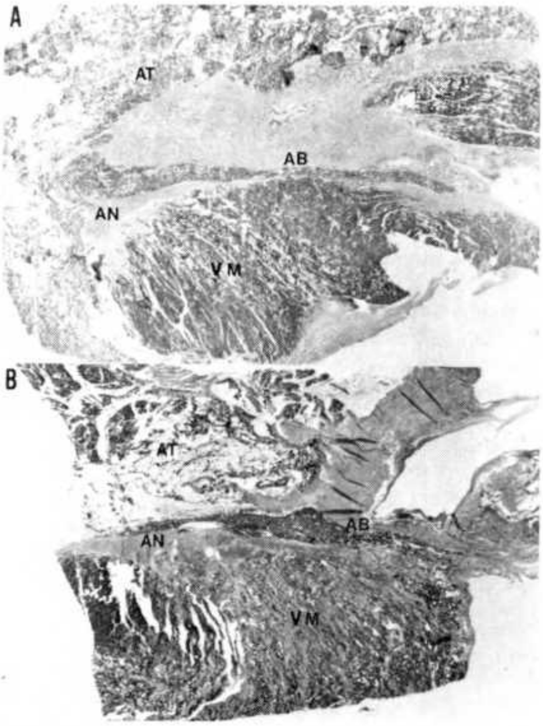

Fig. 2 (A) *A normal atrioventricular node (AN) can be seen between the atrial (AT) and the ventricular (VM) muscle. The proximal node, at the end of the structure, is surrounded by collagenous tissue (pale staining). Along the entire course of the node this tissue separates the node from both atrium and ventricle. As the node is followed distally (toward the right) it blends into the atrioventricular bundle (AB). (Haematoxylin, phloxine, and tartrazine × 6 original magnification.)* (B) *In contrast, a typical atrioventricular node and atrioventricular bundle of a patient with progressive systemic sclerosis. The node is flattened and narrow, particularly in the proximal area. (Haematoxylin, phloxine, and tartrazine × 6 original magnification.)*

In this case there had been complete heart block with narrow QRS complexes on the electrocardiogram for several years.

The proximal portion of the right bundle-branch was normal in both branching pattern and structure except in the case with complete heart block, in which it was large but could not be traced back to the common bundle. The branching patterns of the proximal portions of the left bundle appeared normal in all the cases except the one in which there was complete heart block. The left bundle emerged from the common bundle over a relatively wide area.

Discussion

The advantage of our technique in sectioning the atrioventricular node is threefold. Firstly by doing so parallel to the long axis we cut through about a millimetre of right ventricular endocardium and then through the one and half millimetres of node. Thus an entire atrioventricular node and bundle study is contained in many fewer sections. Traditional methods section at right angles to the long axis and the node, bundle, and origin of the bundle-branches is nearly 15 mm long, as opposed to 1·5 mm in the plane in which we section. Secondly we can more easily compare sections from different subjects by using the right-sided endocardial surface as a reference point. We can then measure accurately the distance from the surface to the conducting system structures. The third advantage is that in the particular plane in which we view the structures we can in appropriate section see the outline of the node, bundle, and part of the branching system. This technique does not jeopardise, however, microscopical analysis.

We found that in one case there was discontinuity between the penetrating portion of the atrioventricular node and bundle. This discontinuity was probably the cause of the clinical finding of complete heart block in this case. All the cases, however, showed a remarkably consistent finding—namely, that while the microscopical structure of the proximal atrioventricular node appeared to be within normal limits, the macroscopical appearance was not. The normally bulbous, pear-shaped proximal end was long and narrow.

We believe that this is probably a manifestation of progressive systemic sclerosis. There is no doubt that the patients had the disease for long periods and that, as shown in Table 2, the heart was involved in all of them.

We also have electrocardiographic evidence that in two of these seven cases there was evidence of atrioventricular block, though we cannot unequivocally attribute the block to the morphological change seen in the atrioventricular node. Certainly in the single patient with complete block there was other histological evidence, the discontinuity between the node and the bundle, but this patient, too, had a narrow proximal portion of the node. The other six all had abnormal nodes but only one had a prolonged PR interval and it was for this reason we undertook a parallel study to look for more subtle evidence of atrioventricular nodal damage. The 12 lead electrocardiogram is inadequate in this respect, for though a long PR interval may indicate atrioventricular nodal disease, a long intra-atrial conduction time and a long His to Purkinje conduction time may also be responsible for this.[11] Indeed, a prolonged atrioventricular nodal conduction time can be masked by a short His-Purkinje conduction time and thus give a normal

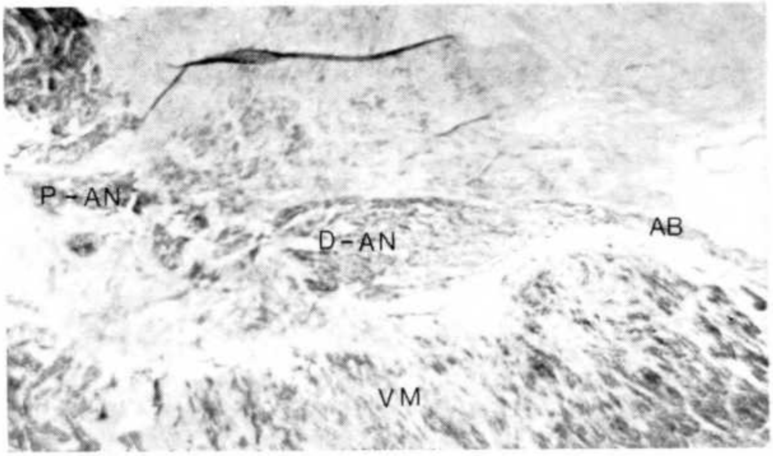

Fig. 3 *The atrioventricular nodal area and atrioventricular bundle (AB) in a patient with progressive systemic sclerosis and complete heart block. The proximal atrioventricular node (P-AN) has degenerated. The distal atrioventricular nodal (D-AN) area is well formed and blends into the atrioventricular bundle. Ventricular muscle (VM) is seen inferiorly to the node. (Haematoxylin, phloxine, and tartrazine. Original magnification ×12).*

PR interval.[12] In fact we found that eight of the nineteen patients had impaired atrioventricular nodal conduction and a further three had conduction which was at the upper limits of normal. Two other patients, however, had an abnormally brief conduction time through the atrioventricular node.

It is uncertain whether both the decreased and the enhanced conduction can be explained by the change we describe in the proximal portion of the node. In the rabbit's atrioventricular node, a structure similar to the human one, the greatest conduction delay occurs in the most proximal portion.[13] The major morphological changes in the atrioventricular node that we have observed are in the proximal region. Thus a reduction in the size of this area by fibrous replacement may cause relatively quicker atrioventricular nodal conduction, when conduction is intact, because of the reduction of the slowest area of conduction. Increased fibrosis around the proximal end of the atrioventricular node may also be responsible for the relatively common finding of prolonged atrioventricular nodal conduction or prolonged atrioventricular nodal refractory periods. The milieu in which enhanced and slowed atrioventricular nodal conduction occurs may be conducive to tachyarrhythmias. Indeed, James[5] speculates that atrioventricular nodal changes could be responsible for a high frequency of supraventricular tachycardias.

References

1 Windesheim JH, Parkin TW. Electrocardiograms of ninety patients with acrosclerosis and progressive diffuse sclerosis (scleroderma). *Circulation* 1958; **17:** 874–81.

2 Oram S, Stokes W. The heart in scleroderma. *Br Heart J* 1961; **23:** 243–59.

3 Escudero J, McDevitt E. The electrocardiogram in scleroderma. Analysis of 60 cases and review of the literature. *Am Heart J* 1968; **56:** 846–55.

4 Lev M, Landowne M, Matchar JC, Wagner JA. Systemic scleroderma with complete heart block. *Am Heart J* 1966; **72:** 13–24.

5 James TN. De subitaneis mortibus. VIII. Coronary arteries and conduction system in scleroderma heart disease. *Circulation* 1974; **50:** 844–56.

6 Ridolfi RL, Bulkley BH, Hutchins GM. The cardiac conduction system in progressive systemic sclerosis. Clinical and pathologic features of 35 patients. *Am J Med* 1976; **61:** 361–6.

7 Roberts NK, Pepin D. The atrioventricular node, His bundle and bundle branches—a new histologic technique. *Stain Technol* 1977; **52:** 131–5.

8 Lev M, Widran J, Erickson EE. A method for the histopathologic study of the atrioventricular node, bundle and branches. *Arch Pathol* 1951; **52:** 73–83.

9 Masi AT, Rodnan GP, Medsger TA Jr, *et al.* Clinical criteria for early diagnosed systemic sclerosis: preliminary results of the ARA multicenter cooperative study. *Arthritis Rheum* 1978; **21:** 576–7.

10 Winterbauer RH. Multiple telangiectasia, Raynaud's phenomenon, sclerodactyly, and subcutaneous calcinosis: a syndrome mimicking hereditary hemorrhagic telangiectasia. *John Hopkins Hosp Bull* 1964; **114:** 361–83.

11 Roberts NK. *The cardiac conducting system and the His bundle electrogram.* New York: Appleton-Century-Crofts, 1975: 122–5.

12 Roberts NK, Perloff JK, Kark RAP. Cardiac conduction in the Kearns-Sayre syndrome. *Am J Cardiol* 1979; **44:** 1396–1400.

13 Hoffman BF, Paes de Carvalho A, Mello WC, Cranefield PF. Electrical activity of single fibers of the atrioventricular node. *Circ Res* 1959; **7:** 11–8.

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Multiple valve replacement with pericardial xenograft
Clinical and haemodynamic study

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SUMMARY Multiple valve replacement with pericardial xenografts (sizes 17 to 31) was undertaken in 76 patients. The incidence of early and late deaths was 10·5 and 3·9 per cent, respectively. Actuarially it is predicted that 94·7±3·9 per cent of hospital survivors will be alive at three and a half years after valve replacement. Though long-term anticoagulants were not used, thrombotic valve obstruction was not seen in this series. A systemic embolus occurred early in one case only (0·95 episodes/100 patient years). Mechanical dysfunction of the pericardial xenograft has not been seen.

Haemodynamic studies were performed in seven patients, eight to 21 months after valve replacement. The transvalvular gradients were negligible across the aortic pericardial xenografts. Gradients across mitral and tricuspid xenografts were small. The calculated surface areas ranged from 1·0 to 1·4 cm^2 for aortic, 1·7 to 2·1 cm^2 for mitral, and 2·0 to 2·4 cm^2 for tricuspid valves.

These results after multiple valve replacement are comparable to those reported with isolated mitral or aortic pericardial xenografts over a similar period of observation.

Glutaraldehyde stabilised pericardial xenografts have been used for single valve replacement for more than eight years with very good clinical and haemodynamic results.[1–6] Since 1976, when the pericardial xenograft became generally available, it has been used for all the valve replacements at our institution. This preliminary report describes the clinical and haemodynamic experience with 76 patients who underwent multiple valve replacement with the Ionescu-Shiley pericardial xenograft.

Patients and methods

Since March 1971, pericardial xenografts have been implanted in 506 patients. Of these, 430 have had single valve replacement (230 aortic, 196 mitral, and 4 tricuspid). Seventy-six patients have had multiple valve replacement, all between April 1976 and September 1979. The present study describes the clinical and haemodynamic follow-up of these 76 patients who received a total of 160 pericardial xenografts (Table 1).

All valves used were manufactured by a standardised process.* There were 25 men and 51 women and the mean age was 50·0±1·4 years (range 26 to 68). The preoperative clinical details of the patients are shown in Table 2. All valve replacement operations were performed using total body hypo-

Table 1 *Number of patients and valves replaced*

Valves replaced	*No. of patients*
Mitral and aortic	54
Mitral and tricuspid	14
Mitral, aortic, and tricuspid	8
Total	76

Table 2 *Preoperative clinical details of 76 patients with multiple valve replacement*

	Number	*Per cent*
Men	25	33
Women	51	67
Age (y):		
Mean	50·0 ±1·4	
Range	26–68	
NYHA class:		
II	5	7
III	54	71
IV	17	22
Rhythm:		
Sinus	20	26*
Atrial fibrillation	56	74
Previous cardiac surgery	26	34
Valve replacement and repair	6	
Closed mitral valvotomy	19	
Mitral and aortic valve replacement	1	

* All patients in sinus rhythm had mitral and aortic valve disease.

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* Shiley Laboratories Inc, Irvine, California, USA.

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Table 3 *Sizes of pericardial xenografts implanted in 76 patients*

Valves	*Annulus diameter (mm) of implanted xenografts*								*Total*
	17	*19*	*21*	*23*	*25*	*27*	*29*	*31*	
Mitral					16 (2)	40 (4)	17 (1)	3	76 (7)
Tricuspid						8 (2)	10 (2)	4 (2)	22 (6)
Aortic	3	19 (2)	25 (2)	12	3				62 (4)
Total	3	19	25	12	19	48	27	7	160

Figures in parentheses represent the number of valves of each type in patients subjected to reinvestigation.

thermia (20 to 26°C) with cold cardioplegia and topical hypothermia. The temperature of the interventricular septum was maintained by these combined measures between 16 and 18°C. The annulus diameter of the pericardial xenografts implanted ranged from 17 to 31 mm (Table 3). Annuloplastic procedures were not performed irrespective of the size of the aortic root. At the time of valve replacement, 39 additional surgical interventions were undertaken in 33 patients, as shown in Table 4.

All patients received oral sodium warfarin from the second or third postoperative day for a period of four to six weeks. The prothrombin time was maintained around or below twice normal. Long-term anticoagulation was not used.

All patients were seen at six-monthly intervals after operation. Seven patients were reinvestigated between eight and 21 months (mean 12 months) postoperatively. Three had had mitral and tricuspid, one mitral and aortic, and three mitral, aortic, and tricuspid valve replacement. The criteria for selection for reinvestigation were the availability of complete preoperative haemodynamic and angiographic data and the informed consent of the patients. The annulus diameters of the pericardial xenografts investigated are shown in Table 3.

Table 4 *Additional surgical procedures undertaken at time of valve replacement*

Procedure	*Number*
Aortocoronary saphenous vein bypass graft	11
Tricuspid annuloplasty	7
Resection of hypertrophied left ventricular outflow tract	8
Epicardial pacemaker implantation	3
Closure of atrial septal defect	2
Resection and tailoring of ascending aorta	1
Obliteration of left atrial appendage	2
Decalcification of left atrial wall	1
Removal of left atrial clot	2
Repair of femoral artery aneurysm	1
Repair of lacerated superior vena cava	1
Total procedures	39 (33)*

* Figure in parentheses denotes the number of patients.

Right and left heart catheterisation was performed in the fasting state without prior sedation. All patients with an aortic valve replacement underwent transseptal catheterisation as well. Cardiac output was obtained by the direct Fick method. Both peak and ejection systolic gradients across aortic pericardial xenografts were measured. The ejection systolic gradient was obtained by planimetric integration of simultaneously recorded phasic left ventricular and aortic root tracings. The mean diastolic gradient across mitral and tricuspid xenografts was measured by planimetric integration of simultaneously recorded phasic ventricular and pulmonary wedge or right atrial tracings, respectively. The xenograft surface area was calculated according to the hydraulic formula of Gorlin and Gorlin[7] using ejection systolic and mean diastolic gradients. Ventricular and/or aortic root angiograms were performed in all patients.

Actuarial analysis for the expected survival rate and for individual event-free curves of reoperation and thromboembolism was carried out using the method of Anderson *et al.*[8] For the calculation of survival rate hospital deaths were excluded. Standard formulae were used for statistical analysis.

Results

HOSPITAL MORTALITY

There were eight (10·5%) early deaths (within 30 days of the operation) and none of them was related to valve failure. Six patients died from cardiac causes which were: myocardial failure in three instances, ventricular arrhythmia in two, and myocardial infarction in one. The other two deaths were caused by gastrointestinal haemorrhage in one patient and renal failure in another one. Preoperatively, all these patients were in either New York Heart Association class III or IV.

LATE MORTALITY

There were three (3·9%) late deaths, at three, five, and 12 months after operation. The causes of death were urinary tract infection and Gram-negative septicaemia, myocardial failure, and cardiac failure after reoperation for bacterial endocarditis.

The actuarial analysis predicts that 94·7 ±3·9 per cent of hospital survivors will be alive at one and at three and a half years after valve replacement (Fig. 1).

The 65 long-term survivors have been followed for a total of 1257 patient months, with a mean individual follow-up of 19·3 months (range three to 42).

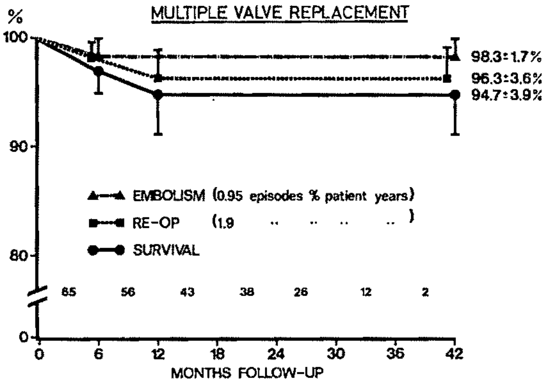

Fig. 1 *Actuarial analysis of results after multiple valve replacement with pericardial xenografts. The data are expressed as percentage of expected survival rate and individual event-free curves. The numbers along the horizontal axis denote the number of patients at the beginning of each six-monthly period. Hospital mortality has been excluded from actuarial calculation.*

THROMBOEMBOLISM

Long-term anticoagulation was not used. One patient (1·3%) with mitral, aortic, and tricuspid valve replacement developed a transient left hemiparesis on the second postoperative day. Actuarially it is predicted that 98·3 ±1·7 per cent of patients will be free from embolism at three and a half years after valve replacement (Fig. 1). Thrombotic valve obstruction has not been encountered in this series.

ENDOCARDITIS

Two patients (2·6%) developed endocarditis, at 12 and 20 months after operation. The first patient was reoperated upon and died in the early postoperative period. The second patient, who developed Rickettsial endocarditis, is undergoing long-term medical treatment, which at the time of writing appears to be controlling the disease.

REOPERATION

Three patients (3·9%) underwent reoperation. One had replacement of the infected pericardial valve, as described above, and two patients had closure of perivalvar (mitral) leak, at five days and 10 months, respectively, after valve insertion. Both these patients are alive and well. 96·3 ±3·6 per cent of hospital survivors are predicted not to need reoperation at one and at three and a half years after valve replacement (Fig. 1).

CLINICAL DATA

Forty-eight of the 65 long-term survivors had been in New York Heart Association class III and 12 in class IV preoperatively; 5 had been in class II. At the latest postoperative visit 39 were now in class I and the remaining 26 were in class II (Fig. 2).

The preoperative cardiothoracic ratio of the entire group was 62·3 ±1·22 per cent and it had decreased significantly to 57·5 ±1·0 per cent ($p < 0·001$) at the latest postoperative visit. On analysis of the three subgroups this high level of significance applied only to those patients with mitral and aortic valve replacement ($p < 0·001$), though the other two subgroups also showed significant reductions in cardiothoracic ratio (Fig. 2).

There were no changes in the proportion of patients with atrial fibrillation (74%) and with sinus rhythm (26%) between the preoperative and the latest postoperative visit. No significant change was noted in either left or right ventricular forces in the electrocardiogram.

HAEMODYNAMIC DATA

The results of the haemodynamic investigations are summarised in Table 5. The cardiac output was normal in patients with either mitral and aortic, or mitral and tricuspid valve replacement, while in

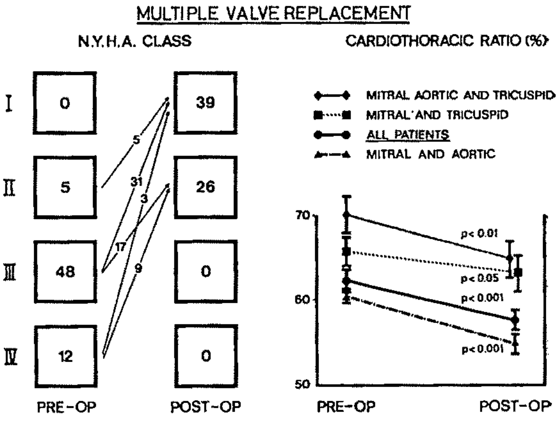

Fig. 2 *Diagrammatic representation of pre- and postoperative New York Heart Association class status and cardiothoracic ratio of 65 long-term survivors.*

Table 5 *Postoperative haemodynamic data (mean values ±SEM) of seven patients with multiple valve replacement*

Valves replaced	*No. of patients*	*CI (l/min per m²)*	*RAP (mmHg)*	*PAP (mmHg)*	*PWP (mmHg)*	*LVEDP (mmHg)*	*Transvalvular gradient (mmHg)*			*XSA (cm²)*		
							*Mitral**	*Aortic†*	*Tricuspid**	*Mitral*	*Aortic*	*Tricuspid*
Mitral and aortic	1	2·7	6	26	17	14	6·4	6·0	—	2·0	1·4	—
Mitral and tricuspid	3	2·6 ±0·6	9·0 ±2·3	28·7 ±3·7	17·4 ±2·0	13·7 ±2·6	6·6 ±0·6	—	2·8 ±0·5	1·9 ±0·1	—	2·2 ±0·1
Mitral, aortic and tricuspid	3	2·4 ±0·2	10·4 ±2·3	31·2 ±5·0	18·6 ±3·0	15·4 ±2·4	6·2 ±1·4	7·0 ±1·0	3·0 ±0·6	1·9 ±0·2	1·3 ±0·2	2·1 ±0·1

Abbreviations: SEM, standard error of the mean; CI, cardiac index; RAP, mean right atrial pressure; PAP, mean pulmonary artery pressure; PWP, mean pulmonary wedge pressure; LVEDP, left ventricular end-diastolic pressure; XSA, calculated xenograft surface area.
* Mean diastolic gradient. † Peak systolic gradient.

patients with triple valve replacement it failed to reach normal levels. The calculated surface area ranged from 1·0 to 1·4 cm^2 for aortic, 1·7 to 2·1 cm^2 for mitral, and 2·0 to 2·4 cm^2 for tricuspid pericardial xenografts. The transvalvular gradients were negligible across the aortic and small across the mitral and tricuspid valves. At angiography all xenografts were found to be competent.

Discussion

Very encouraging long-term clinical and haemodynamic results after isolated mitral or aortic valve replacement with the pericardial xenograft have already been reported,[1–3] but there is no published data concerning the use of the Ionescu-Shiley pericardial xenograft for multiple valve replacement.

The present study has shown very good survival and considerable clinical and haemodynamic improvement in patients with multiple valve replacement up to three and a half years after operation.

The hospital mortality of 10·5 per cent compares favourably with reported data[9–20] and none of the hospital deaths was related to valve failure. All patients who died were in New York Heart Association class III or IV. There were only three late deaths (3·9%) in the present series during the follow-up period and all occurred within 12 months of operation.

Actuarially it is predicted that 94·7 ±3·9 per cent of hospital survivors will be alive at one and at three and a half years after valve replacement (Fig. 1). This actuarial survival rate is similar to the figures reported with either mechanical prostheses[13–16 18 21] or porcine valves[15 17 20 22] for similar periods of follow-up. Fig. 3 shows, for comparison, the survival curves of patients having isolated aortic or mitral valve replacement with pericardial xenografts. Though the duration of follow-up of patients with multiple valve replacement is shorter, the survival curve of this group (for the initial three and a half postoperative years) is comparable to the survival of patients with single valve replacement. This observation is at variance with other reports[18 21 22] which show a lower survival ratio in patients with multiple valve replacement.

Thrombotic valve obstruction, which has been described with mechanical prostheses[18 23] and porcine valves,[21 22 24] has not been encountered with the pericardial xenograft, either with single valve, or in the present series of multiple valve replacement, though long-term anticoagulation was not used. The absence of thrombotic obstruction is the more significant in the present series as it includes 22 patients in whom the tricuspid valve has been replaced. Even though 74 per cent of patients were in chronic atrial fibrillation pre- and postoperatively, there was only one transient

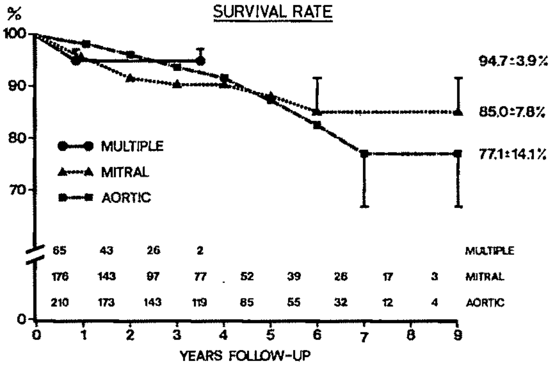

Fig. 3 *Actuarial representation of survival rates in patients with multiple valve and single mitral or aortic valve replacement. The continuous line denotes patients with multiple valve replacement. The broken lines show patients with single valve replacement.*

embolic event (0·95 episodes/100 patient years) in this series and it occurred on the second postoperative day in a patient with triple valve replacement. Actuarially it is predicted that 98·3 ±1·7 per cent of our patients with multiple valve replacement will be free from embolism three and a half years after operation (Fig. 1).

The embolic rate in this series is lower than that reported from patients having multiple valve replacement with either mechanical prostheses[9–14 16 18] or porcine valves.[17 20 22] This low incidence of embolism is comparable with that encountered in patients having single valve replacement with pericardial xenografts and observed for a similar duration of follow-up, as shown in Fig. 4. It is interesting that the embolic episodes in patients with either single or multiple valve replacement with pericardial xenografts all occurred in the first six postoperative weeks,[1 3 25] the only exception being a left fermoral artery embolus 67 months after isolated mitral valve replacement in one patient.[26] The results from this study have reinforced our conviction that long-term anticoagulant treatment in patients with pericardial xenografts is unnecessary, the most likely explanation for the absence of thrombotic valve obstruction and for the very low embolic rate being the superior hydraulic characteristics of this valve compared with the porcine valve.[3 27]

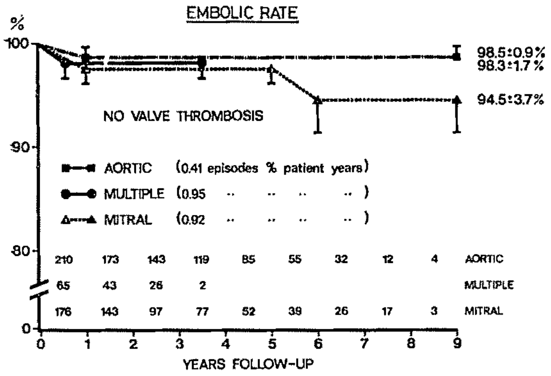

Fig. 4 *Actuarial representation of event-free curves for embolism in patients with multiple valve and single mitral or aortic valve replacement.*

The incidence of endocarditis in this series (1·9 episodes/100 patient years) is similar to that reported with other types of valve replacement.[12–14 16 20]

All patients derived considerable benefit from the operation, 60 per cent being in New York Heart Association class I and 40 per cent in class II at the most recent follow-up.

The haemodynamic investigations performed in seven patients at a mean of 12 months after operation showed normal cardiac outputs at rest. The pulmonary wedge and left ventricular end-diastolic pressures did not return to normal levels, which is not unexpected as all these patients had been in New York Heart Association class III and IV preoperatively. Similar observations have been made by others.[15 19 21] The peak systolic and mean diastolic gradients across the aortic and atrioventricular valves were similar to those which have been obtained in patients with isolated aortic or mitral valve replacement with pericardial xenografts.[4–6] The calculated surface areas of the aortic pericardial xenografts were 1 cm^2 or larger. Thus complicated annuloplastic procedures are unnecessary in patients with a small aortic annulus because of the optimal ratio of implantation diameter to orifice area of the pericardial xenograft valve. The mitral and tricuspid xenografts had areas around 2 cm^2. These data from a small number of patients having multiple valve replacement are similar to those obtained in a larger series of patients with isolated aortic or mitral valve replacement with pericardial xenografts.[5 6] For this reason catheterisation of a larger number of patients with multiple replacements was not considered at this stage.

Table 6 summarises the incidence of major complications in our entire experience with 590 pericardial xenografts inserted in 506 patients. Mechanical dysfunction of the pericardial xenograft

Table 6 *Incidence of significant complications in patients with pericardial xenografts*

			Episodes per 100 patient years			
Valves replaced	*No. of patients*	*Years of follow-up*	*Endocarditis*	*Perivalve leak*	*Embolism*	*Valve dysfunction*
Aortic	230	730	0·55	0·69	0·41	0·96
Mitral	196	542	0·92	0·74	0·92	0·92
Tricuspid	4	22	—	—	—	—
Multiple	76	105	1·9	1·9	0·95	—
Total	506	1399	0·79	0·79	0·64	0·86

has not been observed in either this multiple replacement series or the single replacement series using pericardial xenografts manufactured commercially[3 25] and implanted since April 1976.

In conclusion, this preliminary study of patients with multiple valve replacement has shown a very low propensity for embolism in the absence of long-term anticoagulation and superior haemodynamic performance of the pericardial xenograft when compared with other tissue values.[15 20] Continuous, systematic follow-up of patients with pericardial xenografts will provide the necessary data on progressively longer periods of observation.

References

1 Ionescu MI, Tandon AP, Mary DAS, Abid A. Heart valve replacement with the Ionescu-Shiley pericardial xenograft. *J Thorac Cardiovasc Surg* 1977; **73:** 31–42.

2 Ionescu MI, Tandon AP. Long-term clinical and haemodynamic evaluation of the Ionescu-Shiley pericardial xenograft heart valve. *Thoraxchir Vask Chir* 1978; **26:** 250–8.

3 Ionescu MI, Tandon AP. The Ionescu-Shiley pericardial xenograft heart valve. In: Ionescu MI, ed. *Tissue heart valves.* London: Butterworths, 1979: 201–52.

4 Tandon AP, Smith DR, Mary DAS, Ionescu MI. Sequential haemodynamic studies in patients having aortic valve replacement with the Ionescu-Shiley pericardial xenograft. *Ann Thorac Surg* 1977; **24:** 149–55.

5 Tandon AP, Smith DR, Whitaker W, Ionescu MI. Long term haemodynamic evaluation of aortic pericardial xenograft. *Br Heart J* 1978; **40:** 602–7.

6 Tandon AP, Smith DR, Ionescu MI. Hemodynamic evaluation of the Ionescu-Shiley pericardial xenograft in the mitral position. *Am Heart J* 1978; **95:** 595–601.

7 Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *Am Heart J* 1951; **41:** 1–29.

8 Anderson RP, Bonchek LI, Grunkemeier GL, Lambert LE, Starr A. The analysis and presentation of surgical results by actuarial methods. *J Surg Res* 1974; **16:** 224–30.

9 Bigelow JC, Herr RH, Wood JA, Starr A. Multiple valve replacement. Review of five years' experience. *Circulation* 1968; **38:** 656–63.

10 Midell AI, DeBoer A. Multiple valve replacement. An analysis of early and late results. *Arch Surg* 1972; **104:** 471–6.

11 Pluth JR, Broadbent JC, Barnhorst DA, Danielson GK. Aortic and mitral valve replacement with cloth-covered Braunwald-Cutter prosthesis. *Ann Thorac Surg* 1975; **20:** 239–48.

12 Stephenson LW, Kouchoukos NT, Kirklin JW, Karp RB, Pacifico AD. Combined aortic and mitral valve replacement: results in 251 patients (abstract). *Circulation* 1975; **51** & **52,** suppl II: 31.

13 Åberg B, Henze A, Björk WO, Combined aortic and mitral valve replacement with the Björk-Shiley tilting disc valve prosthesis. *Scand J Thorac Cardiovasc Surg* 1977; **11:** 1–10.

14 Lepley D Jr, Flemma RJ, Mullen DC, Singh H, Chakravarty S. Late evaluation of patients undergoing valve replacement with the Björk-Shiley prosthesis. *Ann Thorac Surg* 1977; **24:** 131–9.

15 Rhodes GR, McIntosh CL. Redwood DR, Itscoitz SB, Epstein SE. Clinical and hemodynamic results following triple valve replacement: mechanical vs procine xenograft prostheses. *Circulation* 1977; **56,** suppl II: 122–7.

16 Stephenson LW, Kouchoukos NT, Kirklin JW. Triple-valve replacement: an analysis of eight years' experience. *Ann Thorac Surg* 1977; **23:** 327–32.

17 Stinson EB, Griepp RB, Oyer PE, Shumway NE. Long-term experience with porcine aortic valve xenografts. *J Thorac Cardiovasc Surg* 1977; **73:** 54–63.

18 Björk VO, Henze A. Prosthetic heart valve replacement. Nine years experience with the Björk-Shiley tilting disc valve. In: Ionescu MI, ed. *Tissue heart valves.* London: Butterworths, 1979: 1–28.

19 Nitter-Hague S, Frøysaker T, Enge I, Rostad H. Clinical and haemodynamic observations after combined aortic and mitral valve replacement with the Björk-Shiley tilting disc valve prosthesis. *Scand J Thorac Cardiovasc Surg* 1979; **13:** 25–31.

20 Oyer PE, Stinson EB, Rossiter SJ, Miller DC, Reitz BA, Shumway NE. Extended experience with the Hancock xenograft bioprosthesis. In: Sebening F, Klövekorn WP, Meisner H, Struck E, eds. *Bioprosthetic cardiac valves.* Munich: Deutsches Herzzentrum München, 1979: 47–59.

21 Melvin DB, Tecklenberg PL, Hollingsworth JF, *et al.* Computer-based analysis of preoperative and postoperative prognostic factors in 100 patients with combined aortic and mitral valve replacement. *Circulation* 1973; **47** & **48,** suppl III: 56–62.

22 Cohn LH, Collins JJ Jr. The glutaraldehyde stabilized porcine xenograft valve. In: Ionescu MI, ed. *Tissue Heart valves.* London: Butterworths, 1979: 173–200.

23 Bonchek LI, Starr A. Ball-valve prostheses: current appraisal of late results. *Am J Cardiol* 1975; **35:** 843–54.

24 Johnson AD, Daily PO, Peterson KL, *et al.* Functional evaluation of the porcine heterograft in the mitral position. *Circulation* 1975; **52,** suppl I: 40–8.

25 Ionescu MI, Tandon AP. Long-term clinical and haemodynamic evaluation of the Ionescu-Shiley pericardial xenograft heart valve. In: Sebening F, Klövekorn WP, Meisner H, Struck E, eds. *Bioprosthetic cardiac valves.* Munich: Deutsches Herzzentrum München, 1979: 199–213.

26 Ionescu MI, Whitaker W, Tandon AP. Mitral valve replacement without long-term anticoagulants (8·5 years experience with pericardial xenograft) (abstract). *Br Heart J* 1980; **43:** 118.

Br Heart J 1980; **44:** 541–4

Secondary carcinoma of left atrium simulating myxoma

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SUMMARY Three cases are presented in which secondary carcinoma in the left atrium mimicked atrial myxoma or infective endocarditis. Constitutional features of weight loss, fever, anaemia, leucocytosis, raised erythrocyte sedimentation rate, and systemic emboli were prominent clinical features. The association of these systemic manifestations with both secondary deposits in the atrium and atrial myxomata may be the result of an immune response to circulating tumour antigens. Mitral stenosis was present in two of the three patients suggesting that left atrial thrombus may provide a site for the seeding of malignant cells.

In patients dying with disseminated secondary carcinoma a detailed and specific search of the heart at necropsy shows that between 5 and 25 per cent have cardiac deposits.[1–3] The most frequent morphological patterns seen are diffuse pericardial deposits and one or more intramyocardial nodules, ranging in size from microscopical foci to those several centimetres across. In contrast to the relatively common pathological finding of cardiac secondaries, significant clinical symptoms or signs are rare. Characteristic clinical presentations include cardiac tamponade,[3 4] constrictive pericarditis,[4] atrial arrhythmias,[3] conduction disturbances,[5] and obstruction to right ventricular outflow.[6] Systemic manifestations of fever, a high erythrocyte sedimentation rate, weight loss, anaemia, and abnormal serum proteins are phenomena usually associated with atrial myxomata,[7 8] and may be found both with and without systemic emboli. We describe three cases in which these systemic manifestations were the presenting features of left atrial deposits from carcinomata.

Case reports

CASE 1

A 72-year-old woman was admitted complaining of breathlessness for two years and sudden loss of movement in the left arm and leg. She was in atrial fibrillation with clinical signs of pulmonary hypertension, a soft opening snap, and a grade 2/4 mid-diastolic murmur. A dense left hemiparesis was noted but there was no splenomegaly, no splinter haemorrhages, and no evidence of emboli in the optic fundi. Investigation showed: Hb 11·3 g/dl; a leucocytosis of 26 800; ESR 92 mm/h; serum Ig G, A, and M all normal; urine analysis, 20 RBC/ mm^3; electrocardiogram, QRS axis +90° and partial right bundle-branch block. A chest *x*-ray film showed left atrial enlargement with dilated pulmonary veins. An echocardiogram showed left atrial dilatation and typical rheumatic mitral stenosis, with no evidence of left atrial myxoma.

Diagnoses of rheumatic mitral stenosis and cerebral emboli were made. She was treated with anticoagulants and the ventricular rate was controlled with digoxin. The erythrocyte sedimentation rate and total white count showed no change and 20 days after admission a profuse crop of splinter haemorrhages appeared in the left hand and a soft pansystolic murmur was noted. Despite persistently negative blood cultures and a sterile marrow aspirate, a diagnosis of bacterial endocarditis was made. Broad-spectrum antibiotic therapy was initiated, but had no effect, and the patient died.

Necropsy showed moderate rheumatic mitral stenosis (valve orifice 1·8 cm^2). The left atrium was partially occupied by a layer of pale friable thrombus containing abundant malignant cells (Fig. 1). The left adrenal contained a necrotic tumour, 2·5 cm in diameter, extending into the perirenal fat. Cerebral,

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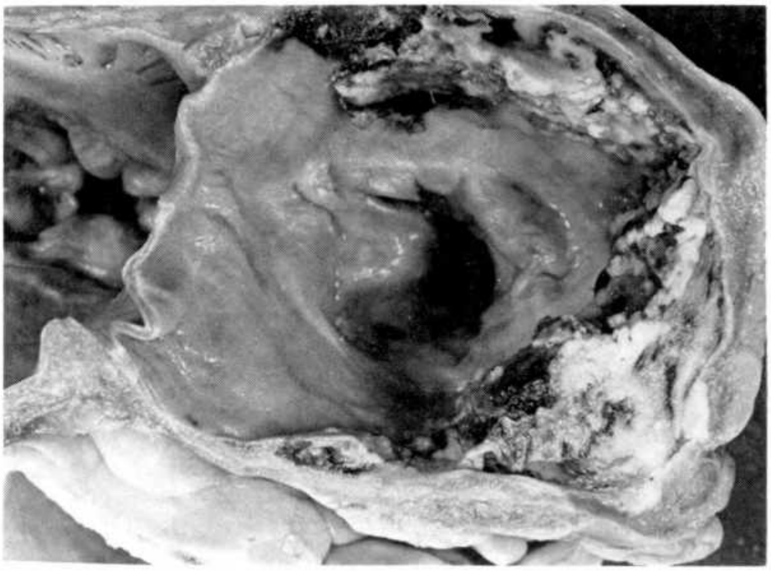

Fig. 1 *Case 1: View of left atrium from above showing friable mural thrombus. Histology showed the presence of numerous malignant cells.*

renal, and splenic emboli consisted largely of tumour cells. Electronmicroscopy showed neurosecretory granules in isolated tumour cells suggesting a primary adrenal medullary tumour.

CASE 2

A 76-year-old woman gave a history of rheumatic fever at the age of 35. She had presented at the age of 74 with severe dyspnoea and was found to have tight mitral stenosis. Mitral valvotomy was carried out and her dyspnoea was dramatically improved. Sixteen months later, however, she became generally unwell with a persistent low grade pyrexia and weight loss. There were persistent and unchanging physical signs of mild mitral stenosis and regurgitation. Investigations showed: ESR greater than 120 mm/h; Hb 8·6 g/dl; total white blood cell count 26 000; alpha-2-globulin increased; fibrinogen increased to 8·3 g/l. Though the patient continued to lose weight and remained pyrexial, blood cultures were persistently negative. An echocardiogram showed a left atrial dimension of 6·3 cm but no detectable myxoma.

Necropsy showed a tumour mass 4·0 cm in diameter within the interatrial septum and eroding into the left atrium where it was covered by thrombus. The mitral valve showed chronic rheumatic valve disease with scarring from a previous valvotomy (orifice 2·5 cm^2). A 6 cm tumour mass was found within the left adrenal extending into perirenal fat. No other tumour deposits were found and the histology suggested a primary malignant adrenal tumour. Electronmicroscopy did not show secretory granules within tumour cells and there was insufficient other evidence to classify the tumour as medullary or cortical.

CASE 3

A 38-year-old woman presented with sudden onset of a mild left hemiplegia, chest pains, and breathlessness. Three years previously she had been treated for stage IIb carcinoma of cervix by radiotherapy. Two weeks after admission to hospital a blotchy skin rash and subungual splinter haemorrhages appeared. Investigations on initial admission showed: Hb 14·1 g/dl; total white cell count 16 400; ESR 60 mm/h. She remained apyrexial throughout. A chest *x*-ray film showed shadowing in the left upper lobe. Lower limb phlebograms did not show venous thrombosis and a lung scan was normal. The clinical diagnoses considered were pulmonary emboli and bacterial endocarditis but blood cultures and serological tests for brucellosis and psittacosis were negative. The patient deteriorated and in view of the previous history of carcinoma and persistent lung shadow it was felt that disseminated malignancy was likely.

Necropsy showed pulmonary lymphatic tumour permeation, metastatic tumour in paracolic, coeliac, and hilar lymph nodes, and small hepatic deposits. The heart was normal apart from a rounded mass, measuring 2 × 1·5 cm, firmly attached to the centre of the atrial surface of the anterior cusps of the mitral valve. The underlying cusp was slightly thickened but with no destruction of valve tissue.

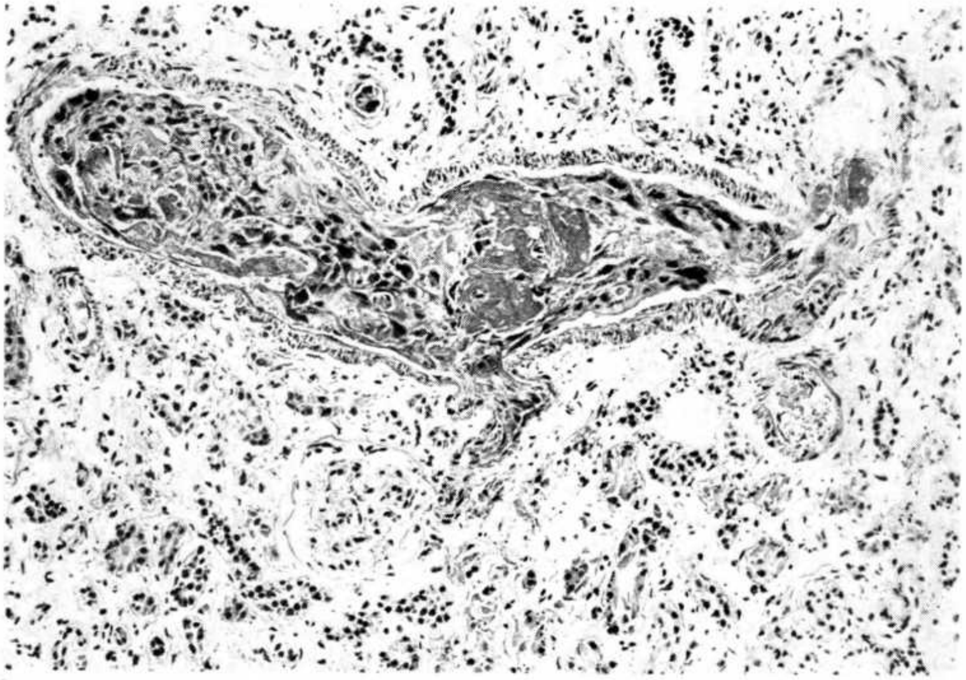

Fig. 2 *Case 3: Photomicrograph showing tumour embolus in a medium sized renal artery.*

Histologically the mass consisted of tumour cells with a superficial covering of thrombus. The kidneys showed one area of infarction which was the result of tumour embolus (Fig. 2).

Discussion

In necropsy series the frequency of myocardial or pericardial secondaries may be as high as 25 per cent because of selection.[2 3] Even in retrospect, however, the majority of patients with cardiac secondaries have no recognisable clinical symptoms or signs. Thus in 302 patients with cardiac secondaries,[3] only six had related symptoms, three with pericardial tamponade caused by malignant effusions and three with atrial tachyarrhythmias associated with intra-atrial tumour deposits.

Glancy and Roberts[4] in a retrospective study of the clinical data of 70 patients with disseminated malignant melanoma could not separate those with and those without cardiac metastases. Thurber and his colleagues[9] reviewed the electrocardiograms of 148 patients who had cardiac secondaries; 48 were abnormal, but in none was the abnormality clearly related to the secondary deposits. Berge and Sievers[1] also failed to show any specific electrocardiographic abnormalities in patients with cardiac secondaries. In some instances, however, myocardial metastases have been shown to produce electrical abnormality simulating ischaemic damage.[10] Thus, the great majority of cardiac metastases are clinically silent and the general systemic manifestations and embolic phenomena found in our three patients have not been previously emphasised.

Systemic manifestations including fever, high erythrocyte sedimentation rate, raised white blood cell count, and increased serum globulins are usually regarded as characteristic of left atrial myxomata and were found in varying combinations in 40 of 45 patients with this condition.[7] The mechanism of these systemic phenomena is obscure[8] but has been linked to either necrosis within the myxoma[11] or an immune response to tumour antigens.[12 13] In the three cases presented here systemic manifestations were associated with secondary carcinoma in the left atrium, and this supports the theory that tumour cells within thrombi in the systemic circulation may be a potent stimulus for an immune response to tumour antigens. Pure thrombus in the left atrium, commonly seen in chronic rheumatic disease, is not associated with such a clinical picture.

The systemic manifestations and embolic phenomena in the cases presented here initially raised the clinical possibility of atrial myxomata. In the first two cases a left atrial mass was apparently excluded by echocardiography. The failure of the echocardiograms to show the tumour mass in these patients probably reflects its sessile nature and its fixation to the atrial wall. After left atrial myxoma, infective endocarditis remained the most likely clinical diagnosis despite negative blood cultures. A case of left atrial metastases from an unrecognised ovarian choriocarcinoma presenting with anaemia, leucocytosis, and a high erythrocyte sedimentation rate posed the same clinical differential diagnostic problems.[14]

In the first two cases it seems likely that circulating tumour cells seeded in a pre-existing left atrial thrombus and subsequently grew into a larger tumour mass. The presence of chronic rheumatic valve disease leading to left atrial thrombus formation was therefore an important common factor in these two patients. In the last case, however, the tumour mass was located on the atrial aspect of the anterior mitral valve cusp rather than in a pre-existing thrombus. In patients with disseminated malignancy, non-bacterial endocarditis is not an uncommon finding. If these marantic (non-bacterial thombotic endocarditis) vegetations are sectioned a tiny proportion is found to contain malignant cells. It seems possible that in our third patient this process provided the nidus for tumour growth, a process which has been aptly named malignant endocarditis.[15] Microscopical malignant vegetations may be more common than is usually realised but probably few patients live long enough to develop a large tumour mass.

References

1 Berge T, Sievers J. Myocardial metastases. A pathological and electrocardiographic study. *Br Heart J* 1968; **30:** 383–90.

2 Fine G. Neoplasms of the heart and pericardium. In: Gould SE, ed. *Pathology of the heart and blood vessels*. 3rd ed. Springfield, Illinois: Charles C Thomas, 1968: 851–83.

3 Davies MJ. Tumours of the heart and pericardium. In: Pomerance A, Davies MJ, eds. *The pathology of the heart.* Oxford: Blackwells, 1975:

4 Glancy DL, Roberts WC. The heart in malignant melonama. *Am J Cardiol* 1968; **21:** 555–71.

5 Redwine DB. Complete heart block caused by secondary tumors of the heart. Case report and review of the literature. *Tex Med* 1974; **70:** 59–64.

6 Griffith DNW, Myers A. Obstruction of right ventricular outflow tract by solitary ovarian metastases. *Br Heart J* 1978; **40:** 700–2.

7 Goodwin JF. Diagnosis of left atrial myxoma. *Lancet* 1963; **i:** 464–8.

8 Greenwood WF. Profile of atrial myxoma. *Am J Cardiol* 1968; **21:** 367–75.

9 Thurber DL, Edwards JE, Achor RWP. Secondary malignant tumors of the pericardium. *Circulation* 1962; **26:** 228–41.

10 Harris TR, Copeland GD, Brody DA. Progressive injury current with metastatic tumor of the heart. *Am Heart J* 1965; **69:** 392–400.

11 MacGregor GA, Cullen RA. The syndrome of fever, anemia and high sedimentation rate with an atrial myxoma. *Br Med J* 1959; **ii:** 991–3.

12 Boss JH, Bechar M. Myxoma of the heart. *Am J Cardiol* 1959; **3:** 823–8.

13 Currey HFL, Mathews JA, Robinson J. Right atrial myxoma mimicking a rheumatic disorder. *Br Med J* 1967; **i:** 547–8.

14 Hepp A, Larbig D, Bader H. Left atrial metastasis of chorion carcinoma, presenting as mitral stenosis. *Br Heart J* 1977; **39:** 1154–6.

15 Coller FC, Inkley JJ, Moragues V. Neoplastic endocardial implants. *Am J Clin Pathol* 1950; **20:** 159–64.

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Fibrinolytic treatment of thrombus on prosthetic heart valves

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SUMMARY Fibrinolytic agents were administered for 13 episodes of thrombus formation on mitral or aortic valvar prostheses in 12 patients. The most common presenting features were pulmonary oedema (six cases) or arterial emboli (six cases). The diagnosis of thrombus formation was made by phonocardiography on the following criteria: (a) modifications of the prosthetic sounds (12 cases), (b) appearance of a valvar obstructive syndrome (10 cases).

The treatment consisted of streptokinase (100 000 units/h after a loading dose, seven cases) or urokinase using either low doses (75 000 to 112 500 units/h, three cases) or moderate doses (150 000 units/h, three cases) for one to four days.

Immediate complete regression of clinical and phonocardiographic anomalies was seen in eight cases. Incomplete improvement was seen in two patients, leading to operation: this was unsuccessful in one patient who had surgery on the third day, and was successful in the other on the 75th day. There were three failures leading to successful reoperative procedures in two patients and to an early death in the third patient suffering from acute myocardial infarction. One non-fatal haemopericardium was observed in a patient treated with streptokinase. No important side effect was noted during delivery in a pregnant woman.

During subsequent follow-up, a recurrent episode of thrombus formation was observed in one patient, treated by fibrinolytic therapy with success. One patient had an operation for a valve replacement six months after fibrinolytic treatment because of non-thrombotic valvar dysfunction; the outcome was fatal. Six patients are alive and in good condition, with a follow-up of six months to five years.

Thrombus formation represents the main late complication of valvar prostheses. Since the first published observation,[1] and the first successful treatment by new valve replacement,[2] many cases have been reported. Emergency surgical treatment, however, may be hazardous under some conditions, with a mortality rate about 50 per cent.[3] Taking into account the first reported successful treatment with streptokinase,[4] we decided to manage such patients initially with fibrinolytic therapy.

Subjects and methods

Twelve patients were treated for 13 episodes of thrombotic obstruction of a prosthetic valve. There were five men and seven women (including one who was 8 months pregnant), with ages ranging from 23 to 69 years (average 51 years).

There were eight Starr-Edwards prostheses of the following types: four series 6120 in the mitral position (including one which was subject to a recurrent episode of thrombus formation in a patient with a chronic pulmonary artery thrombosis); one series 6400 in the mitral position; and three series 1260 in the aortic position. There were four Björk-Shiley prostheses, of which three were in the mitral position and one was in the aortic position.

The presenting features included pulmonary oedema in six cases (acute in three of them), systemic arterial emboli in six cases, angina pectoris in two cases (one of them having had a normal coronary arteriogram four months previously), myocardial ischaemia in one case, and myocardial infarction in two cases (one of them with low cardiac output (Table 1).

All patients received anticoagulant drugs. This

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treatment produced an effect within the therapeutic range in eight episodes (seven patients), with prothrombin times, evaluated with rabbit brain thromboplastin, below 35 per cent. The treatment was inadequate in the other five patients (Table 2).

Table 1 *Clinical manifestations*

Symptoms	*No. of cases*
Acute pulmonary oedema	3
Subacute pulmonary oedema	3
Cerebral emboli	4
Angina pectoris	2
Limb emboli	2
Myocardial ischaemia	1
Myocardial infarction	2
Low cardiac output	1

CRITERIA FOR DIAGNOSIS

The diagnostic criteria were based on the association of abnormal prosthetic sounds and murmurs related to an obstructive syndrome.[5] Phonocardiograms were performed for all patients, using a Mingograf 81 seven-channel direct ink-writing recorder, providing a frequency response from 20 to 800 cycles. Chart speed was 100 mm per s. Carotid pulse was recorded with an EMT 5 105 transducer. Time intervals were corrected according to heart rate using the Bazett formula,[6] and carotid ejection time was calculated as a percentage of normal using the Hartman diagram.[7] Echocardiograms were performed on eight patients, using a Smith-Kline Ekoline 20-A apparatus. These two techniques were performed before, and 12, 24, and 48 hours after fibrinolytic therapy, taking care to use the same amplitude for all traces in the same patient.

The other investigations consisted of cinefluoroscopy (nine patients), left ventriculography (two patients), and left heart catheterisation (one case).

FIBRINOLYTIC TREATMENT

The fibrinolytic treatment used was streptokinase* in seven instances and urokinase in six instances. Urokinase† was chosen in case 3 because of previous allergic symptoms and in case 6 because of recent treatment by streptokinase. In the four other cases, it was an arbitrary choice.

Streptokinase was administered continuously via a peripheral vein with an infusion pump. According to recommendations,[8] an initial dose of 500 000 international units (IU) together with 50 mg hydrocortisone were administered over 30 minutes, followed by 100 000 IU per hour over a period of 12 to 96 hours. As soon as the fibrinogen level exceeded 1·5 g per l, heparin infusion was introduced to bring the patient's recalcification clotting time to at least twice the control value.[9]

Urokinase was administered empirically in the recommended doses, irrespective of body weight. Infusion was by a similar technique, using an

Table 2

Case no.	*Sex*	*Age (y)*	*Weight (kg)*	*Prosthesis*	*Anticoag.*	*Symptoms*	*Diagnosis*	*Treatment*
1	M	47	62	M Björk	Adequate	Acute pulmonary oedema	PCG +, cine 0	SK 4 days
2	F	64	48	Ao Starr	Inadequate	Arterial emboli, myocardial infarction, shock	PCG +, cine 0	UK 1 day, 75 000 U/h
3	M	50	64	Ao Starr	Adequate	Angina pectoris	Coron, PCG +	UK 1 day, 112 500 U/
4	M	54	70	Ao Starr	Inadequate	Cerebral embolism, myocardial infarction	PCG 0, cine 0, cineangio 0	SK 2 days
5	M	59	60	M Starr	Adequate	Subacute pulmonary oedema	PCG +, cine 0, echo 0	SK 1 day
6	Same patient				Adequate	Subacute pulmonary oedema	PCG +, echo 0	UK 2 days, 150 000 U
7	F	68	59	M Björk	Adequate	Acute pulmonary oedema	PCG +, cine ±, echo 0	SK 2 days
8	F	53	51	M Starr	Adequate	Subacute pulmonary oedema	PCG +, cathet +, cine +, echo 0	UK 2 days, 150 000 U
9	M	55	71	M Starr	Inadequate	Cerebral embolism, myocardial ischaemia	PCG +, echo +, cine +	UK 3 days, 300 000 U every 6 hours
10	F	57	56	M Björk	Adequate	Acute pulmonary oedema	PCG +, echo +, cine 0	UK 2 days, 150 000 U
11	F	26	52	M Starr	Inadequate (Pregnancy)	Arterial embolisms	PCG +, cine 0, echo 0	SK 12 hours
12	F	52	61	M Starr	Adequate	Cerebral embolism	PCG +, cine 0, cineangio 0	SK 2 days
13	F	23	52	Ao Björk	Inadequate	Cerebral embolism	PCG +, cine 0	SK 2 days

M, mitral; Ao, aortic; cine, cinefluoroscopy; echo, echocardiography; cineangio, cineangiography; PCG, phonocardiogram; Coron, coronary arteriography; Cathet, left catheterisation. +, Examination typical of thrombus. 0, No sign of thrombosis. ±, Equivocal examination.

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*Streptokinase (Hoechst Laboratories)

†Urokinase (Choay Laboratories)

initial dose of 150 000 IU over 30 minutes, followed by 75 000 to 150 000 IU per hour for 24 to 48 hours. Individual infusion rates were as follows: 75 000 IU per hour (1560 IU/kg) in case 2, 112 500 IU per hour (1760 IU/kg) in case 3, and 150 000 IU per hour in the three other patients (2500 IU/kg in case 6, 2940 IU/kg in case 8, 2680 IU/kg in case 10). Simultaneous heparin infusion was instituted to attain the modifications in the recalcification clotting time. In case 9 urokinase treatment consisted of 300 000 IU every six hours over three days using intermittent intravenous injections: this low dosage did not justify serum fibrinogen level measurements.

Heparin was replaced by oral anticoagulants after seven to 15 days of fibrinolytic therapy.

Results

Clinical details are summarised on Table 2. Diagnosis was made in all cases but one by phonocardiography.

MITRAL PROSTHESES (9 episodes)

(a) Before treatment

There was a positive diagnosis in nine episodes, relying on the following: a conspicuous decrease or disappearance of the opening click (all cases); associated with a prolonged diastolic rumble (cases 5, 6, 7, 8, 10, 11, 12); in cases 5, 6, 7, 8, 10, and 12 carotid ejection time was obviously reduced. In addition a late systolic murmur was noted twice in the patient with recurrent thrombosis (cases 5 and 6).

The traces showed a normal closing click in all patients and, when it could be measured, a normal second sound to prosthetic opening click interval (except for case 1, where it was shortened).

(b) After treatment

In six cases there was complete disappearance of the diastolic rumble as well as any systolic murmur, and recovery of a normal opening click. In case 12, the amplitude of the opening sound remained abnormal. For the last two patients (cases 9 and 10) the phonocardiogram remained unchanged.

AORTIC PROSTHESES (4 episodes)

(a) Before treatment

There was a positive diagnosis in all but one case (case 4) based on the occurrence of the following features compared with reference traces: a prolonged high frequency delayed peak systolic murmur in three patients (cases 2, 3, 13) with a palpable thrill in case 13; a decrease in the amplitude ratio of the aortic opening to the aortic closing sound (Hylen ratio) related to a conspicuously reduced opening click in cases 2 and 3 (in case 13 the association of a predominant decreased closing click led to an increase in this ratio, see Fig. 3); the development of a faint diastolic murmur in cases 2, 3, and 13; and finally the following carotid pulse modifications: increase of ejection time in two cases (3, 13), increase of half-rise time in all cases, and a coexistent slight "aortic stenosis-like" pattern with modification of the incisura in all cases.

(b) After treatment

The phonocardiogram remained completely unchanged in case 2. In the two other diagnosed cases (cases 3 and 13) the traces showed the complete disappearance of all the anomalies.

Other investigations included the following:

ECHOCARDIOGRAPHY (Table 2)

In two out of eight cases abnormal prosthetic motions were noted. In these two (cases 9 and 10) no improvement was seen.

CINEFLUOROSCOPY (Table 2)

Two out of 10 cases (cases 8 and 9) showed a clearly impeded ball excursion. In case 7, it was less obvious. In seven cases it was normal. After treatment, there was an improvement in only one of the two cases with definite abnormality (case 8).

TRANSSEPTAL LEFT HEART CATHETERISATION

This was performed in one case (case 8) and showed

mmediate results	*Follow-up*
uccess	Haemopericardium operated on 12th day; 6 month: surgery (prosthesis dysfunction), death
ailure	Death 24th hour during transfer to surgical centre; necropsy: thrombosis
uccess	Well and alive after 5 years
ailure	Surgery 20th day: thrombosis-Hancock
uccess	2nd thrombosis 75th day
uccess	Death after 2½ years (pneumonia). Necropsy: normal prosthesis
uccess	Well and alive after 3 years
uccess	Well and alive after 2 years
ailure	Surgery 8th day: thrombosis-Starr
ransient clinical improvement	Surgery 3rd day: partial thrombosis lysis; operative death
uccess	Uterine haemorrhage, normal delivery, normal child; Alive and well after 2 years
linical and PCG improvement	Cerebral embolism at 8th day, surgery 75th day: thrombosis-Hancock
uccess	Alive and well after 6 months

a left atrioventricular gradient of 9 mmHg.

LEFT CINEANGIOCARDIOGRAPHY

This was performed twice (cases 4 and 12) without producing any positive evidence of thrombus.

EARLY SURGERY (five patients, Table 2) OR A POSTMORTEM EXAMINATION (case 2)

These confirmed thrombus formation in all cases. There were organised thrombi on the rings and on the struts of Starr-Edwards prosthesis in cases 2, 4, 9, and 12 which impeded the motion of the balls. In case 2, an acute myocardial infarction was found with thrombus in the left coronary artery, presumably embolic in origin. In a fifth patient (case 10) a non-organised and non-occlusive thrombus was observed covering a small area of the disc of the Björk-Shiley prosthesis. The surgeon's impression was that the clot was friable, suggesting that partial lysis had occurred. Case 1 was operated upon six months after fibrinolytic treatment and the only surgical finding was dysfunction of the prosthesis. Case 6 died later from pneumonia. The prosthesis was normal.

FIBRINOLYTIC TREATMENT

In seven cases fibrinolytic treatment was with streptokinase and in six cases with urokinase.

Clinical course

The clinical course is set out in Table 2. For those treated with streptokinase, there were four immediate complete successes with a follow-up in the survivors of three years (case 7), two years (case 11), and six months (case 13). The fourth patient (case 1) was initially improved but developed progressive dyspnoea that led to late reoperation. Dysfunction of the prosthesis was found and the patient died after operation.

Of the three other cases treated with streptokinase, there was one initial success with complete clinical improvement, but thrombus formation recurred two and a half months later, leading to a second successful course of fibrinolytic treatment using urokinase (case 5); case 12 showed incomplete clinical and phonocardiographic improvement, leading to a successful reoperation on the 75th day; case 4 had a complete failure of fibrinolytic treatment but successful reoperation on the 20th day.

For those patients treated with urokinase there were three complete successes, with a follow-up of five years (case 3), two and a half years (case 5), and two years (case 8). In case 10 the clinical improvement was only transient, leading to reoperation on the third day, with surgical death.

For the last two cases there was complete failure of treatment: case 2, who suffered from myocardial infarction with cardiogenic shock, died 24 hours later before operation could be performed. Case 9 was successfully reoperated on a week after presentation. These two patients received very low doses of urokinase on a body weight basis (Table 2).

Fibrinogen levels

These are summarised in Table 3.

For streptokinase the maximal fibrinogen decrease (observed within 24 hours) ranged between 0 and 0·9 g/l in six cases. The fibrinogen level was 1·5 g/l in the seventh case.

For urokinase in the three patients receiving a 150 000 IU per hour dosage (1500 to 3000 IU/kg per hour) the fibrinogen decreased between 2 and 2·8 g/l. It remained unchanged in cases 2 and 3, who were receiving a smaller dose. It was not controlled in case 9 who was receiving intermittent small doses.

No significant correlation exists between this early clinical course, the fibrinogen decrease, and the duration of the treatment. We observed six successes among seven patients with a low fibrinogen level, one success among three patients with unchanged (or probably unchanged: case 9) levels, and two successes among three patients with intermediate levels (Table 3).

COMPLICATIONS

There were two patients with haemorrhage. Case 1 developed a haemopericardium after treatment with streptokinase for four days. A predisposing lesion was postoperative pericarditis, clinically diagnosed before administration of streptokinase on the following criteria: pericardial rub heard a week before thrombus formation and increase of cardiothoracic ratio after operation. Pericardio-

Table 3 *Fibrinogen levels*

Case no.	*Treatment*	*Fibrinogen (g/l)*		*Immediate results*
		Before treatment	*After treatment*	
1	SK	4·5	1·5	Success
2	UK	4·8	4·5	Failure
3	UK	6·2	5·9	Success
4	SK	2·7	0·8	Failure
5	SK	4·8	0·8	Success
6	UK	5·0	2·8	Success
7	SK	3·2	0·9	Success
8	UK	4·1	2·3	Success
9	UK	Not done	Not done	Failure
10	UK	3·9	2·0	Failure
11	SK	6·0	0	Success
12	SK	2·7	0·6	Success
13	SK	4·4	0·5	Success

SK, streptokinase; UK, urokinase.

centesis was successfully performed on the 12th day after treatment with streptokinase. Case 1 bled from the uterus during delivery and caesarean section was required.

Discussion

All types of prosthetic valves may develop thrombus, particularly the most commonly used: Starr-Edwards prostheses;[10 11] Björk-Shiley prostheses;[12 13] Lillehei-Kaster prostheses.[14]

This complication appears to be more frequent in the atrioventricular than in the aortic position. Its frequency is reduced by using effective anticoagulant treatment.[15] Nevertheless in eight out of 13 instances included in this paper thrombus formations occurred in spite of adequate treatment. The diagnosis may be suspected in any case with sudden reappearance of signs of valvar obstruction, especially pulmonary oedema, acute coronary insufficiency, and/or systemic arterial embolism.

In our experience, the most reliable positive contribution to the diagnosis of a thrombosed prosthesis is provided by the phonocardiogram. The alteration in the prosthetic clicks, especially the opening click, as first stressed for mitral prostheses by Spencer,[2] led to a positive diagnosis in 12 out of 13 instances of thrombus formation (92%). But the specific element of the obstructive type of dysfunction relies on the association with the prosthetic sound alterations of an obstructive phonocardiographic syndrome as previously described.[7] The main features of this syndrome are the appearance of a prolonged diastolic rumble for atrioventricular valves and of a delayed peak high frequency "stenotic like" systolic murmur with carotid pulse changes for the aortic prostheses. This phonocardiographic obstructive syndrome was present in 10 out of 13 patients (77%). In the mitral position, where thrombus formation is the usual cause of obstruction, prolonged diastolic rumble is always abnormal. Its significance is completely different from that of the brief functional rumble which may be heard on normal prostheses. Its diagnostic value is particularly important with the Björk prosthesis, often characterised by a faint or even absent opening click which does not *per se* indicate dysfunction.[7] This fact underlines the need for a careful recording technique to detect the abnormal rumble of malfunctioning prostheses, using an adequate gain, adequate frequencies (chiefly mid-frequencies), and sometimes manoeuvres to enhance the murmur (left lateral position, exercise, amyl nitrite). As for the second sound to opening click interval variation, it was unreliable in our study; the same applies to the closing sound and to regurgitant murmurs.

For aortic prostheses (especially of the Björk-Shiley type), the wide variation from patient to patient in the ratio of intensity of opening sound to closing sound calls for caution in the clinical interpretation of this as an isolated physical sign in the absence of previous phonocardiographic control. An apparent increase of this ratio may be present paradoxically even in the presence of valve dysfunction as a result of a predominant decrease in the closing click, as shown in our case 13 (Fig. 3). In the same way, slight isolated indentations on a carotid pulse tracing may exist with a normally functioning aortic Björk prosthesis and are not diagnostic of obstruction unless associated with timing abnormalities and systolic murmur modifications; it is essential to follow the latter since the systolic murmur observed with Björk prostheses may be somewhat longer and peak later than the one seen with Starr-Edwards prostheses. All these factors underline the diagnostic value of the association of several signs of obstruction, and also the need for systematic postoperative control tracings.

Despite similar phonocardiographic features, the thrombotic origin of the obstruction can be distinguished from aortic ball variance[16] by the effect of fibrinolytic therapy. The therapeutic improvement may be followed with serial phonocardiograms which may show regression of the auscultatory anomalies and modifications of the carotid ejection time (increases for thrombolysis in the mitral position and decreases for thrombolysis in the aortic position). We found that unchanged measurements implied persistent thrombus. Though very sensitive for the types of prostheses included in this paper, our phonocardiographic obstructive criteria may not be applicable to the more recent types of prostheses for which the normal phonocardiographic criteria (sounds as well as murmurs) differ from those of standard valves. This may limit the value of phonocardiographic detection of dysfunction.

Echocardiography provides an interesting contribution to the study of prosthetic valve function, but does not solve all the problems.[17] It may lead to a diagnosis of thrombosis when an abnormal prosthetic motion is displayed,[18] especially when compared with a previous recording.[19] Moreover, echocardiography may be usefully associated with phonocardiography for the identification of an opening sound which is delayed,[20] or inapparent, as for example with a Lillehei-Kaster prostheses,[14] For mitral prostheses with a short second sound to mitral valve opening interval, the study of the left ventricle and septal motion can help in distinguishing between paravalvar regurgitation, left ventricular malfunction, and prosthetic obstruction.[14 21] In our patients, however, only two of eight recordings suggested thrombotic obstruction. Perhaps the introduction of cross-sectional echocardiography will lead to improved assessment.

It has been suggested that cinefluoroscopy may help when it shows alteration in the motion of a prosthetic valve. It was evident in only two of our patients, and doubtful in two other cases. Since the introduction of a radio-opaque marker in the recent Björk-Shiley prosthetic discs the correct identification of altered motion suggesting thrombotic obstruction may be easier.

Other investigations are invasive. Catheterisation may be useful. A right heart catheterisation may be performed easily using a Swan-Ganz catheter, but when an increase in the capillary wedge pressure exists it does not differentiate between left heart failure and prosthesis dysfunction. This does not apply to left heart catheterisation, which strongly suggests the diagnosis when a gradient is present, as in our case 8. Cineangiocardiography has also helped diagnosis in cases of aortic prostheses dysfunction.[12] These invasive procedures are difficult to perform however and make later fibrinolytic therapy hazardous.

Surgical cure of prosthetic thrombosis involves either simple thrombectomy, or more often the insertion of a new prosthesis. It does not prevent recurrent thrombosis as shown in Inberg's observation[22] and in our case 7. The risk is also considerable when operation is performed as an emergency procedure. In d'Allaines series,[3] it resulted in eight deaths (all but one emergency operations) out of 16 patients. This 50 per cent mortality rate is higher than that caused by reoperation for paravalvar leak (15 deaths out of 82 patients or 18%), which rarely requires an emergency procedure. The surgical risk of reoperation for thrombosis is lower when the haemodynamic condition is satisfactory.[13]

All these considerations justify the use of fibrinolytic therapy which may be used immediately without important risks even for patients in poor condition. Furthermore, surgery may still be performed if medical treatment fails, though few cases have been reported.[4 22-24] We have been using this treatment routinely since 1972, with satisfactory results. In our study of 13 cases we obtained eight immediate successes with complete disappearance of clinical and phonocardiographic anomalies. We also had two partial successes, one of these patients also surviving. But the possibility of recurrent thrombosis must be kept in mind: case 5 (later case 6) developed a second thrombus 75 days after the first course of treatment and was successfully treated with urokinase.

Our experience of six successful cases followed up from six months to five years shows that removal of the prostheses is not necessary after successful fibrinolytic therapy. It may sometimes be desirable to replace a thrombosed prosthesis with a biological valve, but even in such cases initial fibrinolytic therapy may permit better operating conditions and lower mortality.

Fibrinolytic therapy must be given only when a diagnosis of thrombus formation is clearly established by the non-invasive methods described above, and when its effect may be monitored by the same techniques over the first 24 hours. The absence of improvement must lead to reoperation, which may be performed two hours after fibrinolytic activity has been neutralised using protease inhibitors.

The choice of fibrinolytic drug, as well as the dosage, is still debated: either streptokinase or urokinase may be used in moderate (1500 to 3000 IU/kg per hour) or high (4400 IU/kg per hour)[25] doses. We prefer to use streptokinase because of its lower cost and its proven efficiency, but urokinase will be prescribed more often for allergic patients, or after previous treatment using streptokinase. Though our study does not lead to any definite therapeutic recommendations, it seems that most of the successes have been observed when the fibrinogen level was below or equal to 1·5 g/l (six out of seven patients). We had only one successful case among the three patients with high fibrinogen levels. This fact should favour the use of streptokinase or a high dose of urokinase.

The most serious complication was haemorrhage which occurred in two of our patients. In both cases, a predisposing factor was present: haemopericardium developed in a patient with clinically diagnosed postoperative pericarditis, and vaginal bleeding occurred during delivery in the other patient.

As for the return to anticoagulant treatment, we believe that heparin should usually be given as soon as the fibrinogen level reaches 1·5 g/l, generally within 24 to 48 hours of the beginning of fibrinolysis. Later on, if no operation has been done, oral anticoagulant therapy should be resumed. Non-invasive monitoring should be performed at close intervals, at least for the first year, for an early detection of recurrent thrombus formation.

Illustrative case histories

CASE 3

A 50-year-old man, weighing 64 kg, was operated on in March 1973 for aortic valve stenosis. Preoperative coronary angiography gave normal findings. A Starr-Edwards prosthesis (1260) was inserted. Control of postoperative anticoagulant therapy (ethyldicoumarol) seemed satisfactory.

In July 1973, angina pectoris suddenly occurred and lasted until December 1973. At that time the patient was unable to hear the prosthetic sounds, and had no other symptoms. Thrombotic dysfunction of the prosthesis was diagnosed with the phonocardiogram on 17 December. The fibrinogen level was 6·2 g/l. Because of iodine allergy, another coronary arteriogram was not performed. Fibrinolytic therapy using urokinase was undertaken on the 18 December (112 500 IU/h, 1760 IU/kg per hour, over 24 hours). On 19 December, the patient again became aware of prosthetic sounds and the phonocardiogram returned to normal. The fibrinogen level was 5·9 g/l. Angina ceased and the patient has remained free of symptoms until now.

CASES 5 AND 6

A 59-year-old man weighing 60 kg underwent surgery in November 1974 for rheumatic mitral stenosis with atrial fibrillation, associated with a chronic right pulmonary artery thrombosis. A Starr-Edwards prosthesis of series 6120 was inserted. Subsequent anticoagulant treatment using acenocoumarol was apparently effective.

In October 1975, progressive subacute pulmonary oedema appeared with simultaneous decrease in prosthetic sounds. Cinefluoroscopy and an echocardiogram of the prosthesis remained normal, but the phonocardiogram indicated a diagnosis of thrombus involving the prosthesis. The fibrinogen level was 4·8 g/l.

On 5 November, thrombolytic therapy using streptokinase was undertaken over 24 hours. By 6 November, pulmonary oedema had regressed. The patient noted the reappearance of his prosthetic sounds, and the phonocardiogram became normal (Fig. 1). The fibrinogen level was 0·8 g/l. In spite of appropriate anticoagulant treatment, subacute pulmonary oedema recurred on 15 January 1976, and prosthetic sounds ceased. The phonocardiogram showed the same abnormal features as in November 1975, whereas the echocardiogram was again normal. The fibrinogen level was 5 g/l.

On 21 January, a second course of fibrinolytic treatment using urokinase (150 000 IU/h, 2500 IU/kg per hour, over 48 hours) was undertaken (Fig. 2). All the symptoms had disappeared by the 23 January. The fibrinogen level was 2·8 g/l. The phonocardiogram regressed to normal. The patient received the same anticoagulant therapy as previously and remained free of symptoms until August 1978. He then died because of a pulmonary infection and septicaemia. Necropsy ruled out any dysfunction of the prosthesis.

CASE 7

A 68-year-old woman weighing 59 kg underwent commissurotomy for mitral stenosis in 1957, followed by insertion of a Starr-Edwards mitral prosthesis (6120) in 1966. Apparently effective anticoagulant therapy was given using phenindione. The first occurrence of thrombus on the prosthesis necessitated operation on 30 December 1975 (insertion of a Björk-Shiley prosthesis). Subsequent anticoagulant therapy was in the therapeutic range.

On 14 February 1976, subacute pulmonary oedema occurred. Clinical examination disclosed a decrease in the amplitude of the prosthetic sounds. Echocardiogram was normal, whereas cinefluoroscopy gave equivocal results. Phonocardiogram led to the diagnosis of thrombosis. The prothrombin ratio was 27 per cent, and the fibrinogen level was 3·2 g/l.

On 15 February thrombolytic therapy using streptokinase was given for 48 hours. The fibrinogen level was 0·9 g/l after 12 hours and 1·7 g/l 48 hours later.

In spite of the patient becoming aware of valve sounds and regression of pulmonary oedema, the treatment had to be continued for a second 24 hour period until phonocardiographic anomalies disappeared completely. Valve function remains normal, with a follow-up of three years.

CASE 11

A 26-year-old woman, weighing 52 kg, underwent surgery in 1975 for mitral stenosis with insertion of a Starr-Edwards (6400) prosthesis. In 1976 she was pregnant, and in the eighth month of pregnancy anticoagulant therapy consisted of calcium heparinate. This treatment was ineffective. At the ninth month, two episodes of aphasia occurred and on 28 January 1977 the patient was admitted for an axillary embolism. Cinefluoroscopy and echocardiography were normal, but phonocardiography led to diagnosis of thrombotic involvement of the valve. The fibrinogen level was 6 g/l.

Treatment using streptokinase was undertaken. During the third hour, the signs of axillary embolism disappeared but a transient episode of aphasia occurred. Twelve hours after treatment was started a uterine haemorrhage occurred, with rupture of the membranes. The fibrinogen level was 0. Streptokinase was stopped and fibrinogen and protease inhibitors were prescribed. A

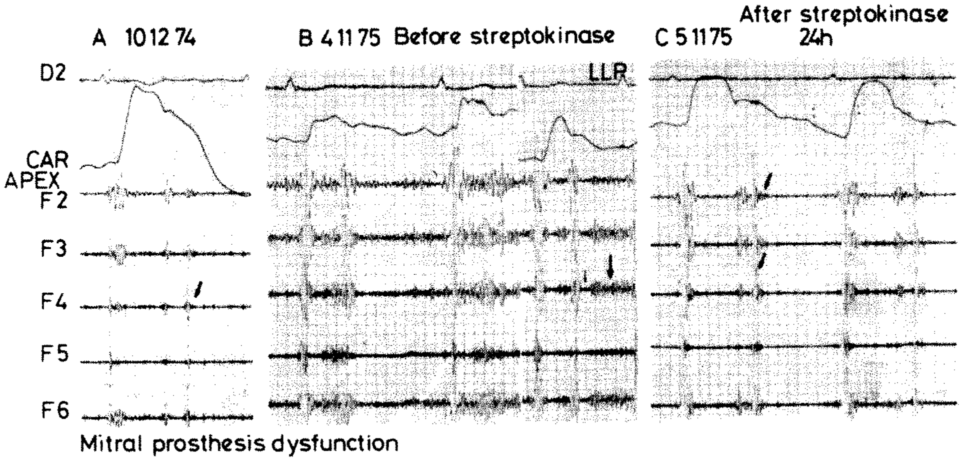


Fig. 1 *(case 5)—Starr-Edwards mitral prosthesis no. 6120. Obstructive dysfunction.* From top to bottom: *electrocardiogram, lead II; carotid pulse; apex phonocardiograms (F2 low frequencies, F3 middle frequencies, F4 middle high frequencies, F5 high frequencies, F6 audible frequencies). Chart speed 100 mm/s. LLP, left lateral position.* (A) *10/12/74: postoperative control phonocardiogram. Normal function as assessed by the closing and opening prosthetic click* (arrows): *amplitude is clearly greater than that of the second sound. Diastole free of vibrations. Ejection time 85 per cent of normal.* (B) *4/11/75: the disappearance of the opening click associated with the delayed* (little arrow) *prolonged diastolic rumble enhanced by left lateral position, led to the diagnosis of obstruction, reflected in the decrease in the carotid ejection time (70% normal). Also late systolic murmur and increased pulmonary component of second sound.* (C) *5/11/75: after 24 hours of streptokinase all the anomalies disappeared, the opening click* (oblique arrow) *reappeared, and carotid ejection time increased to 85 per cent of normal.*

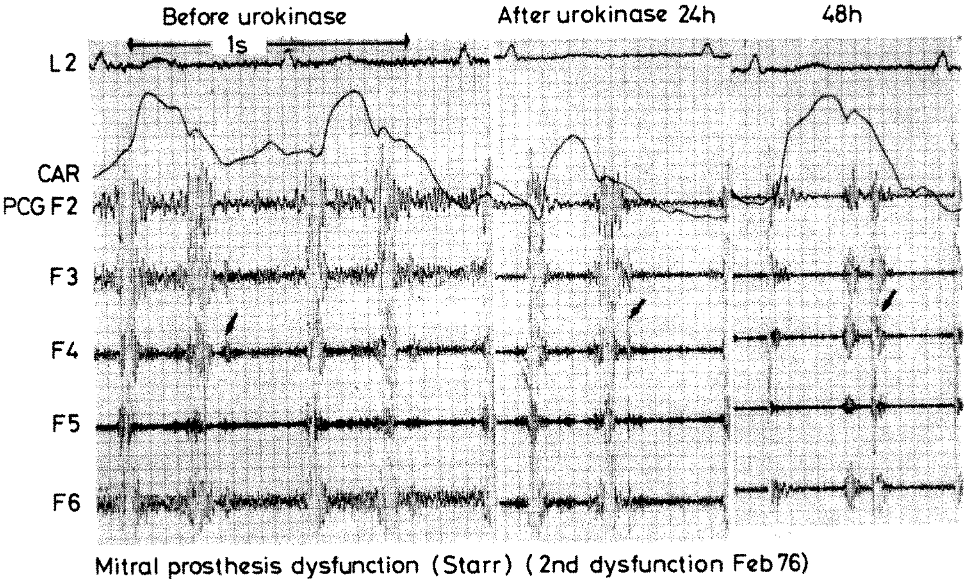
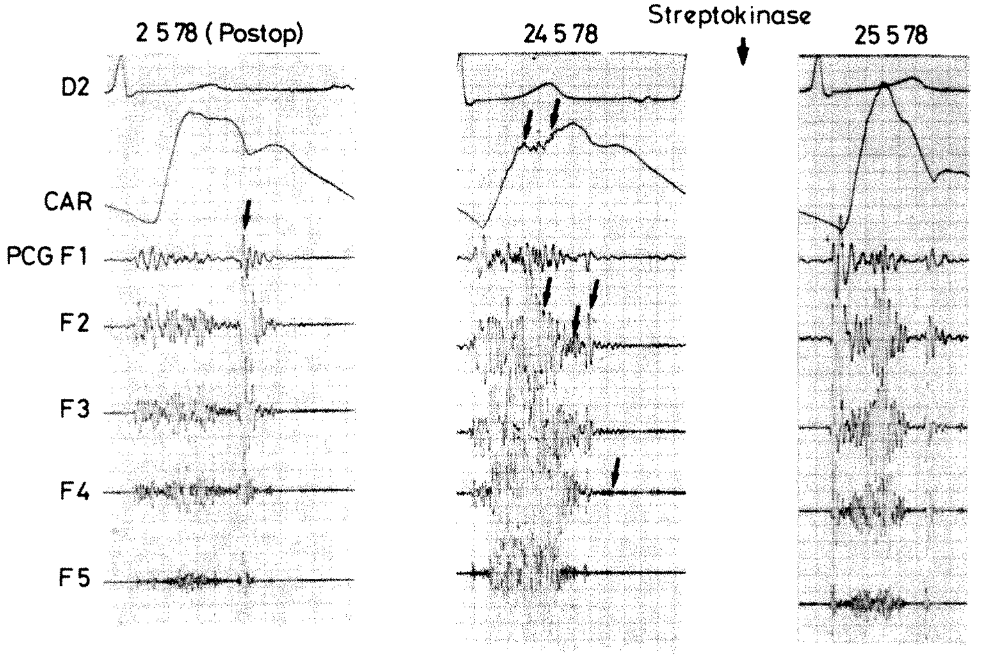

Before urokinase
1s
After urokinase 24h
48h
L2
CAR
PCG F2
F3
F4
F5
F6
Mitral prosthesis dysfunction (Starr) (2nd dysfunction Feb76)

Fig. 2 *Same patient, recurrent dysfunction of the Starr-Edwards prosthesis. Same abbreviations as Fig. 1. Before urokinase the same conspicuous anomalies reappeared. After 24 hours of treatment, the improvement was considerable. Though there was incomplete persistence of systolic and diastolic vibrations, increase in pulmonary component of second sound, and carotid ejection time was still reduced (85% of normal). After 48 hours of urokinase, the phonocardiogram returned to normal with a normal opening click amplitude and a normal carotid ejection time (95% of normal).*



Aortic Björk prosthesis thrombosis

Fig. 3 *(case 13)—Aortic Björk prosthesis dysfunction. 2/5/78: postoperative control phonocardiogram. Normal function: a normal aortic Björk prosthesis phonocardiogram often involves a slightly prolonged systolic murmur, an AO/AC ratio clearly less than 1 (here 0·34), and some irregularities of the carotid pulse pattern. The systolic murmur is mainly displayed on the middle frequency, and rapidly decreases after its systolic peak. The ejection time (100%) and the half-rise time (0·047 s) are normal. Normal sequence of the second sound components. In diastole, there is discrete mitral opening snap resulting from previous mitral commissurotomy. 24/5/78—the diagnosis of dysfunction is assessed by the changes* (oblique arrows) *in the systolic murmur, in the amplitude of the click compared with that of the murmur (clearly less) and in the pattern and timing of the carotid pulse (ejection time: 125% of normal, half-rise time 0·074 s) leading to paradoxical splitting of the second sound. Note an unusual increase in the AO/AC ratio (0·46) caused by the simultaneous alteration of the two prosthetic clicks. There was also a faint diastolic murmur, and a systolic thrill. 25/5/78—after 24 hours of streptokinase there was improvement in the pattern of the carotid trace (ejection time 105% of normal, half-rise time 0·054 s) and phonocardiographic anomalies. Because of the clear increase of the closing click, the AC/AO ratio has paradoxically returned to 0·20 though dysfunction no longer existed.*

caesarean section was performed and the newborn child was normal. Heparin was started again 10 hours later. The phonocardiogram performed the following day was normal.

Subsequently, the patient again received acenocoumarol with a satisfactory follow-up of two years.

References

1 Garamella JJ, Lynch MF, Schmidt WR, Jensen JK. Fatal clotting of the Starr-Edwards mitral ball valve nineteen months post operatively. *Cardiovasc J Thorac Surg* 1964; **47:** 673–80.

2 Spencer FC, Trinckler JF, Reeves JT. Successful replacement of a thrombosed mitral ball prosthesis. *JAMA* 1965; **194:** 1249–51.

3 d'Allaines Cl, Le Guerrier A, Dubost Ch. Fréquence et gravité des réinterventions sur les prothèses valvulaires intracardiaques. *Coeur Med Interne* 1978; **17:** 183–9.

4 Luluaga IT, Carrera D, d'Oliviera J. *et al.* Successful thromybolytic therapy after acute tricuspid valve obstruction (letter). *Lancet* 1971; **i** 1067–8.

5 Veyrat C, Kalmanson D, Witchitz S, Seban Cl, Senikies A, Chiche P. Diagnostic phonomécanographique des dysfonctionnements de prothèses valvulaires par obstruction. *Coeur Med Interne* 1975; **14:** 265–83.

6 Bazett JJ. An analysis of the time relations of electrocardiograms. *Heart* 1920; **7:** 353–70.

7 Hartman H. The external carotid artery tracing. *Memorial del 4è Congr. Tomo 1 B, Mexico.* 1962: 437.

8 Brogden RN, Speight TM, Avery GS. Streptokinase: a review of its clinical pharmacology, mechanism of

action and therapeutic uses. *Drugs* 1973; **5:** 357–445.
9 Conard J, Samama M. *Laboratory control of SK therapy in present status of thrombosis. International Symposium on intravascular coagulation and fibrinolysis, Sherbrooke 1972.* Stuttgart: FK Schattauer Verlag, 1973: 191–8.
10 Sarin Cl, Yalav E, Clement AJ, Brainbridge MV. Thromboembolism after Starr valve replacement. *Br Heart J* 1971; **33:** 111–4.
11 Barnhorst DA, Oxman HA, Connoly DC, *et al.* Long-term follow-up of isolated replacement of the aortic or mitral valve with the Starr-Edwards prosthesis. *Am J Cardiol* 1975; **35:** 228–33.
12 Ben-Zvi J, Hildner FJ, Chandraratna PA, Samet P. Thrombosis on Bjork-Shiley aortic valve prosthesis. *Am J Cardiol* 1974; **34:** 538–44.
13 Fernandez J, Samel A, Yang SS, *et al.* Late thrombosis of the aortic Bjork-Shiley prosthesis. *Chest* 1976; **70:** 12–16.
14 Brodie BR, Grossman W, McLaurin L, Starek PJK, Craige E. Diagnosis of prosthetic mitral valve malfunction with combined echophonocardiography. *Circulation* 1976; **53:** 93–100.
15 Vidne B, Erdman S, Levy MS. Thromboembolism following heart valve replacement by prosthesis: survey among 365 consecutive patients. *Chest* 1973; **63:** 713–7.
16 Louis P, Duzer A, Faure D, Bouhey J. La "maladie de la bille" des valves de Starr aortiques. *Coeur Med Interne* 1970; **9:** 263–80.
17 Feigenbaum H. *Echocardiography*. 2nd ed. Philadelphia: Lea and Febiger, 1976: 199–213.
18 Bernal-Ramirez JA, Phillips JH. Echocardiographic study of malfunction of the Bjork-Shiley prosthetic heart valve in the mitral position. *Am J Cardiol* 1977; **40:** 449–53.
19 Berndt TP, Popp RL. Echocardiographic and phonocardiographic confirmation of suspected caged mitral valve malfunction. *Chest* 1976; **70:** 221–30.
20 Pfeiffer J, Goldschlager N, Sweatman T, Gerbode F, Selzer A. Malfunction of mitral ball valve prosthesis due to thrombus. *Am J Cardiol* 1972; **29:** 95–9.
21 Miller HC, Gibson DG, Stephens JD. Role of echocardiography and phonocardiography in diagnosis of mitral paraprosthetic regurgitation with Starr-Edwards prostheses. *Br Heart J* 1973; **35:** 1217–25.
22 Inberg MV, Havia T, Arstila M. Thrombolytic treatment for thrombotic complication of valve prosthesis after tricuspid valve replacement. *Scand J Thorac Cardiovasc Surg* 1977; **11:** 195–8.
23 Witchitz S, Veyrat C, Moisson P, Kalmanson D, Chiche P. Thromboses tardives des prothèses valvulaires mitrales et tricuspidiennes. Diagnostic phonomécanographique et traitement. *Ann Cardiol Angeiol* 1974; **23:** 399–409.
24 Baille Y, Choffez J, Sicard MP, *et al.* Traitement fibrinolytique des thromboses de prothèse valvulaire. *Nouv Presse Med* 1974; **3:** 1233.
25 American Heart association Urokinase pulmonary embolism trial. A national cooperative study. Monograph no. 39 *Circulation* 1973; **47 & 48:** Suppl 2: 7–108.

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Limitations of two frame method for displaying regional left ventricular wall motion in man

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SUMMARY Regional abnormalities of left ventricular function are frequently determined from superimposed cavity outlines at end-diastole and end-systole. The timing of end-diastole is standardised with respect to the electrocardiogram, but that of end-systole is undefined, and frequently determined by simple inspection. To examine the effect of variation in the timing of the end-systolic frame on apparent regional wall motion, 35 left ventricular angiograms from patients with ischaemic heart disease were digitised frame by frame, and the timing of aortic valve closure and mitral valve opening superimposed on contour displays. In 15 patients, the pattern in the two frame display with end-systole taken as aortic valve closure was similar to that when it was taken as mitral valve opening. In the remaining 20, however, there were major discrepancies between the two, because of changes in cavity shape during isovolumic relaxation. These shape changes were the result of asynchronous termination of systole in different regions of the ventricle. In addition, there was a significant increase in left ventricular cavity area of 3·9±1·7 per cent during isovolumic relaxation, corresponding to an increase in calculated volume of 8·1±4·5 per cent. Estimates of ejection fraction derived from end-systole taken at end-ejection were thus consistently greater than those at mitral valve opening. These differences in the apparent pattern of regional wall motion resulting from lack of definition of end-systole are large compared with those reported after intervention angiography, or surgery. Thus, if two frame methods are to be used, the timing of end-systole must be standardised. We suggest that end-ejection be used. Changes of shape during isovolumic relaxation should be considered separately.

Regional abnormalities of left ventricular wall movement are a significant feature of coronary artery disease, so that their detection and documentation by angiography forms an essential part of the assessment of such patients. A left ventricular angiogram, however, contains so much information that it is not usually possible to assimilate it all using purely manual methods. For this reason, it has become customary to demonstrate regional left ventricular wall movement by superimposing end diastolic and end-systolic cavity outlines.[1] If the only abnormalities of wall movement were those of amplitude, such a display would be adequate, provided that the timing of the two frames was appropriate. In practice, however, this method appears to have limitations. While end-diastole can be determined either with reference to the electrocardiogram or the onset of tension development, end-systole, even in the normal subject, is undefined. In coronary artery disease, the timing as well as the amplitude of wall motion may be abnormal. In particular, in ischaemic myocardium, the duration of tension development may be prolonged,[2] so that end-systole occurs at different times in different parts of the same ventricle. We have therefore investigated possible limitations in the two frame technique for displaying regional wall motion arising from this lack of definition of end-systole. We have varied the timing of the end-systolic frame within the period of isovolumic relaxation and have examined the effect on regional wall movement as displayed by the two frame method.

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Subjects and methods

Left ventricular angiograms from 120 patients who had undergone cardiac catheterisation for assessment of ischaemic heart disease were reviewed. Of these, the timing of aortic valve opening and closure was apparent in 35. In these cases, the cusps were visible within the aortic root. The timing of aortic valve opening was taken as the frame in which the cusps had just begun to lift and separate. Complete opening had usually occurred by the succeeding frame. Aortic valve closure was taken as apposition of the cusps, this frame usually being preceded by one showing them in the half closed position. Mitral valve opening was taken as the first frame showing unopacified blood within the left ventricular cavity from the left atrium.[3]

Left ventriculograms were performed during diagnostic cardiac catheterisation. A bolus of 40 ml contrast was injected into the ventricle at 15 ml/s, with the patient in the right anterior oblique position. A film speed of 50 frames/s was used. Ectopic and post-ectopic beats were not studied. Calibration was by means of a grid exposed at mid-chest level. The left ventriculograms were digitised frame by frame.[3] The following information was derived:

(1) A continuous plot of cavity area, and volume, derived using the regression equation of Dodge *et al.*[4]

(2) The time of minimum cavity area.

(3) The change in area and calculated volume between aortic valve closure (AVC) and mitral valve opening (MVO).

(4) Values of ejection fraction, calculated using the frame synchronous with aortic valve opening as end-diastolic, and end-systolic taken as (a) the frame synchronous with aortic valve closure (EF.AVC), or (b) with mitral valve opening (EF.MVO).[5]

(5) A pair of two frame displays, with the end-diastolic outline in both taken as that synchronous with aortic valve opening, and end-systolic as (a) that of aortic valve closure, or (b) of mitral valve opening.

The apparent pattern of regional wall motion on the two displays was compared, and discrepancies between the two were noted. Particular attention was paid to the following.

(a) Reversal of systolic wall motion between the two, that is one display showing regional inward and the other outward movement affecting the same area.

(b) Differences in the regional amplitude of movement between the two displays, amounting to more than 5 mm. This figure was chosen on the grounds that differences of this magnitude, observed as the result of an intervention, would probably be regarded as clinically significant.

The statistical significance of differences between means was assessed, where appropriate, by Student's t test. Linear regression was performed by the method of least squares fit.

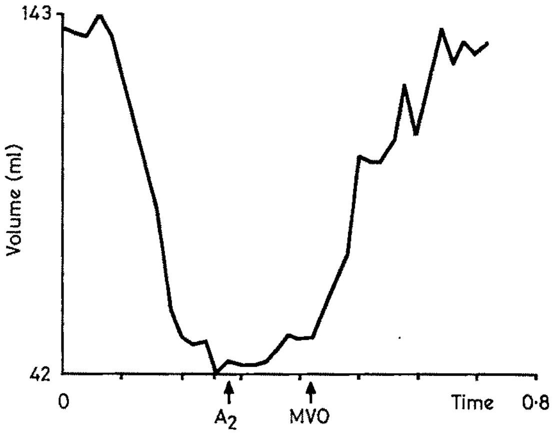

Fig. 1 *Normal left ventricular volume plot from a cineangiogram. The timing of A2 (aortic valve closure) and MVO (mitral valve opening) are indicated. There is an increase in calculated volume between the two.*

Results

(1) CHANGE IN CAVITY AREA AND VOLUME DURING ISOVOLUMIC RELAXATION

There was a consistent increase in cavity area during the period between aortic valve closure and mitral valve opening (Fig. 1) of 3·9 ±1·7 per cent, which was significantly different from zero ($p < 0{\cdot}001$). This corresponded to an increase in cavity volume of 8·1 ±4·5 per cent. In patients with regional abnormalities of wall movement during isovolumic relaxation,[3] the increase in area was 4·5 ±1·4 per cent, significantly greater than the value of 3·0 ±1·6 per cent found in those without such abnormalities ($p < 0{\cdot}01$).

(2) EFFECT OF TIMING OF END-SYSTOLE ON CALCULATED LEFT VENTRICULAR EJECTION FRACTION

As a result of the apparent change in cavity volume between the times of aortic valve closure and mitral valve opening, there were consistent differences in ejection fraction resulting from these differing values of end-systolic volume. The mean value of ejection fraction with end-systole taken as aortic valve closure (EF.AVC) was 68·3 per cent, and as mitral valve opening (EF.MVO) was 59·9 per cent. The corresponding regression equation was:

$$(\text{EF.MVO}) = 0{\cdot}98\ (\text{EF.AVC}) - 7{\cdot}2 \text{ per cent}$$

$r = 0{\cdot}96$, and the standard error of the estimate was 4·9 per cent. The intercept differed significantly from zero ($p < 0{\cdot}05$). Estimates of ejection fraction

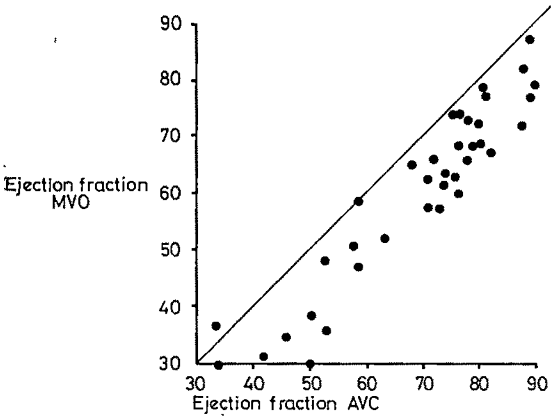

Fig. 2 *Comparison of estimates of ejection fraction, taking end-systole as mitral valve opening (MVO) and aortic valve closure (AVC).*

calculated when end-systole was taken as mitral valve opening were thus significantly lower than when aortic valve closure was used (Fig. 2).

(3) DISCREPANCIES IN ASSESSMENT OF REGIONAL WALL MOTION

The two displays, one with end-systole taken as the time of aortic valve closure and the other as that of mitral valve opening, agreed in describing wall motion in 15 patients. In eight of these, contraction pattern was normal, and ejection fraction (AVC) lay between 67 and 87 per cent. In four patients there was generalised hypokinesis, with values of ejection fraction (AVC) between 24 and 57 per cent. In only three of these patients were regional abnormalities of wall movement present, involving the anterior wall in two and the apex in one. In the remaining 20, however, there were major discrepancies between the two displays (Fig. 3 and 4). In eight, outward movement was shown by one of the pair suggesting an aneurysm, but not by the other. This involved the apex in three, the anterior wall in two, and the inferior wall in a further three. An example is given in Fig. 4. In four patients, the display showing outward movement was that with end-systole taken as synchronous with aortic valve opening (AVC display), and in four it was with end-systole taken as synchronous with mitral valve opening (MVO display). More commonly, however, discrepancies between the two displays related to apparent regional hypokinesis. In 10, the anterior wall was involved, and in all, the apparent abnormality was present on the MVO display. The inferior wall was involved in six. In three the amplitude of wall motion was lower on the AVC display, and in three on the MVO display. The apex was involved in three cases and, as with the anterior wall, the reduced amplitude of wall motion was seen in the MVO display. Both anterior and inferior walls were involved in three patients.

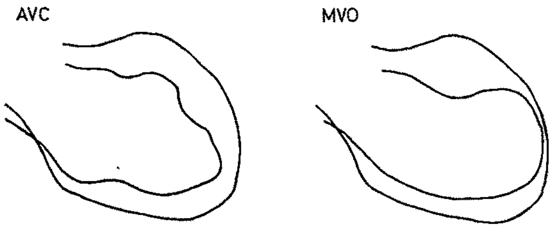

Fig. 3 *Comparison of two frame displays of regional left ventricular wall motion from a single cardiac cycle. End-diastolic outlines are identical, but end-systole was taken as AVC on the left, and MVO on the right. Wall motion on the left appears normal, but hypokinesis is demonstrated on the right.*

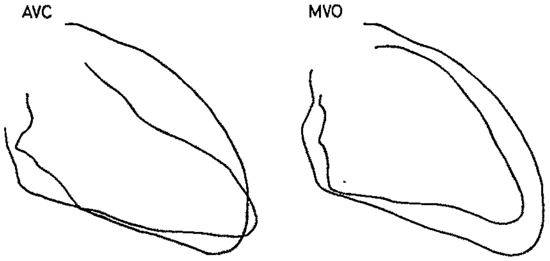

Fig. 4 *Comparison of two frame displays from a single beat. Layout as Fig. 3. Aneurysmal movement at the apex on the left-hand display can be compared with generalised hypokinesis on the right.*

(4) RELATION BETWEEN TIMING OF MINIMUM CAVITY AREA AND THAT OF AORTIC VALVE CLOSURE

Since cavity area increases during isovolumic relaxation, it seemed possible that minimum cavity area might be used to gain some idea of the timing of aortic valve closure if this was not visible on the angiogram. The results are shown in Fig. 5. Though the two were synchronous in 10 patients, there was considerable scatter, with differences of four or five frames, corresponding to time intervals of 80 to 100 ms.

Discussion

In view of its relative simplicity, the two frame technique seems to have much to recommend it as a means of displaying regional left ventricular wall motion. Indeed, it has been extensively used, and

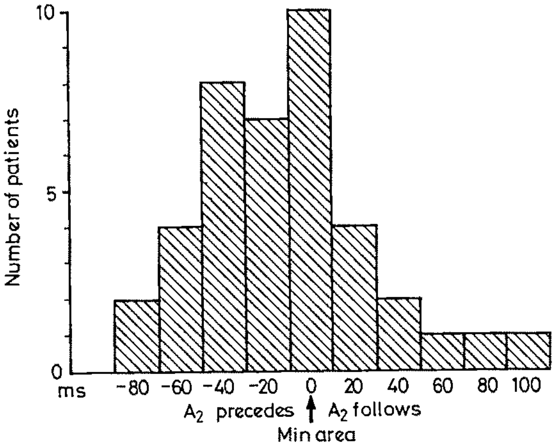

Fig. 5 *Histogram plot showing the relation between aortic valve closure and minimum cavity area shown by the arrow.*

forms the basis of the classification of abnormal wall movement that is still in widespread use.[1] It has also been used to express the results of intervention angiography, an increase in the amplitude of regional wall movement resulting from post-extrasystolic potentiation,[5] administration of glyceryl trinitrate,[6 7] exercise,[8] or catecholamines[9] being taken as evidence of reversible ischaemia. The method has been used to document acute changes in wall motion brought about by atrial pacing,[10] and has been elaborated to quantify wall motion along a series of transverse or radial axes using complex data handling techniques.[11 12] It has also been used to assess the results of surgery.[13]

The present results suggest that the interpretation of two frame displays may not be entirely straightforward. Discrepancies caused by variation in the timing of end-systole are the result of changes in cavity shape during the period of isovolumic relaxation. These changes have been studied in detail by a number of authors,[3 14 15] and are shown to be of two types. A primary abnormality appears to be prolongation of inward wall movement, behaviour often shown by the myocardium within the territory of a diseased coronary artery. Associated with this is premature outward movement elsewhere in the cavity, usually affecting the anterior wall or, less commonly, the apex. This early outward movement is accompanied by premature thinning of the wall and is not therefore the result of overall movement of the heart in space.[16] Myocardium showing this behaviour frequently shows normal systolic behaviour, so that its outward movement is assumed to be the result of inward movement elsewhere in the cavity at a time of constant left ventricular volume.

These considerations stress the difficulty of defining the timing of the end of systole. Changes of cavity shape during isovolumic relaxation indicate that contraction ends asynchronously, being prolonged in those ischaemic areas which show delayed inward movement, and normal, or even short, in those moving outward early. "Systole" thus ends at different times at different places in the cavity, and end-systole as a single event has no meaning. There is no more reason for taking its timing as synchronous with aortic valve closure than with mitral valve opening, and, indeed, with as much reason one could take any other arbitrary time between the two.

The mechanism of changes of shape discussed above has important applications to the determination of the pathological significance of local abnormalities of wall movement. A regional reduction in amplitude is frequently taken as evidence of segmental myocardial disease or depression of function. If the end-systolic frame, however, is taken towards the end of isovolumic relaxation, than an apparent reduction in regional amplitude on a two frame display can result from early outward movement and not from failure of contractile function at all. This was commonly seen in the present series of patients, particularly when it affected the anterior wall or the apex, so that of the 16 cases with apparent hypokinesis affecting these regions, the wall had, in fact, shown normal inward movement during ejection in 13. Uncertainty as to the timing of end-systole can thus lead beyond a simple failure of quantification to misinterpretation of the pathological significance of apparently disturbed wall motion.

Although the major errors resulting from the lack of definition of end-systole come from uncertainty in the detection and interpretation of regional wall motion, a second problem is in the determination of ejection fraction. This is the result of an apparent increase in left ventricular volume immediately before mitral valve opening, as shown by Ruttley and his colleagues.[15] Ejection fraction is an empirical measurement that is very widely used to assess left ventricular function, yet its significance is not defined in physical terms. Though the correlation coefficient between determinations based on end-systole as aortic valve closure and mitral valve opening was very high, values taken with the latter timing were consistently smaller by approximately 8·5 per cent.

The changes in cavity shape and apparent volume described above are large enough to cause uncertainty in the interpretation of wall motion abnormalities in the control state. Though we have not investigated the question in detail, they are large compared with those commonly reported as the result of intervention angiography. If, for example, the display shown in Fig. 3 (left) had followed glyceryl trinitrate administration, a post-ectopic pause, or even an operation, and that shown in Fig. 3 (right) had represented the control state, then erroneous conclusions might readily be drawn. Similarly, an error in resting ejection fraction of 8·5 per cent would probably not lead to clinical mismanagement, but might be considered significant if it had followed the administration of a drug, or some other intervention. It is clear, therefore, that standardisation is required. We would reiterate (Wiggers[17]) that the term end-systole should not be used since it is undefined, and that end-ejection should be substituted. End-ejection can be unambiguously determined from aortic valve closure, and detected non-invasively as the onset of the first high frequency component of the aortic component of the second sound. In the present series, aortic valve closure was visible angiographically in rather a small proportion of patients, but this was a retrospective series, and we have no doubt that the number could have been increased by appropriate positioning and exposure. Unfortunately, the timing of minimum cavity area cannot be rigorously used as a substitute, because of its sensitivity to small errors in the determination of cavity area. We suggest, therefore, that if overall amplitude of wall motion is to be measured, this should be done over a well defined period in the cardiac cycle, preferably ejection. Changes in cavity shape during isovolumic relaxation should be considered separately. The conclusion is difficult to avoid, however, that regional wall motion abnormalities cannot be assessed comprehensively using two frame methods, however elaborate, and that frame by frame analysis is essential for an adequate description of these complex disturbances in patients with ischaemic heart disease.

References

1 Klein MD, Herman MV, Gorlin R. A hemodynamic study of left ventricular aneurysm. *Circulation* 1967; **35:** 614–30.

2 Tyberg JV, Parmley WW, Sonnenblick EH. In-vitro studies of myocardial asynchrony and regional hypoxia. *Circ Res* 1969; **25:** 569–79.

3 Gibson DG, Prewitt TA, Brown DJ. Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. *Br Heart J* 1976; **38:** 1010–9.

4 Dodge HT, Sandler H, Baxley WA, Hawley RR. Usefulness and limitations of radiographic methods for determining left ventricular volume. *Am J Cardiol* 1966; **18:** 10–24.

5 Dyke SH, Cohn PF, Gorlin R, Sonnenblick EH. Detection of residual myocardial function in coronary artery disease using post-extrasystolic potentiation. *Circulation* 1974; **50:** 694–9.

6 Helfant RH, Pine R, Meister SG, Feldman MS, Trout RG, Banka VS. Nitroglycerin to unmask reversible asynergy. Correlation with post coronary bypass ventriculography. *Circulation* 1974; **50:** 108–13.

7 McAnulty JH, Hattenhauer MT, Rösch J, Kloster FE, Rahimtoola SH. Improvement in left ventricular wall motion following nitroglycerin. *Circulation* 1975; **51:** 140–5.

8 Sharma B, Goodwin JF, Raphael MJ, Steiner RE, Rainbow RG, Taylor SH. Left ventricular angiography on exercise. A new method of assessing left ventricular function in ischaemic heart disease. *Br Heart J* 1976; **38:** 59–70.

9 Horn HR, Teichholz LE, Cohn PF, Herman MV, Gorlin R. Augmentation of left ventricular contraction pattern in coronary artery disease by an inotropic catecholamine. The epinephrine ventriculogram. *Circulation* 1974; **49:** 1063–71.

10 Pasternac A, Gorlin R, Sonnenblick EH, Haft JI, Kemp HG. Abnormalities of ventricular motion induced by atrial pacing in coronary artery disease. *Circulation* 1972; **45:** 1195–205.

11 Harris LD, Clayton PD, Marshall HW, Warner HR. A technique for the detection of asynergistic motion in the left ventricle. *Comput Biomed Res* 1974; **7:** 380–94.

12 Rickards AF, Seabra-Gomes R, Thurston P. The assessment of regional abnormalities of the left ventricle by angiography. *Eur J Cardiol* 1977; **5:** 167–82.

13 Chatterjee K, Swan HJC, Parmley WW, Sustaita H, Marcus HS, Matloff J. Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease. *Circulation* 1973; **47:** 276–86.

14 Altieri PI, Wilt SM, Leighton RF. Left ventricular wall motion during the isovolumic relaxation period. *Circulation* 1973; **48:** 499–505.

15 Ruttley MS, Adams DF, Cohn PF, Abrams HL. Shape and volume changes during "isovolumetric relaxation" in normal and asynergic ventricles. *Circulation* 1974; **50:** 306–16.

16 Gibson DG, Traill TA, Brown DJ. Changes in left ventricular free wall thickness in patients with ischaemic heart disease. *Br Heart J* 1977; **39:** 1312–8.

17 Wiggers CJ. Studies on the consecutive phases of the cardiac cycle. I. The duration of the consecutive phases of the cardiac cycle and the criteria for their precise determination. *Am J Physiol* 1921; **56:** 415–38.

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Br Heart J 1980; **44:** 560–9

Left ventricular dysfunction—bedside Valsalva manoeuvre

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SUMMARY Thirty-seven patients were evaluated before cardiac catheterisation by bedside physical examination, including Valsalva manoeuvre, to assess the value of the sphygmomanometrically determined arterial pressure responses during the Valsalva manoeuvre and to compare its sensitivity, specificity, and predictive accuracy in the detection of left ventricular dysfunction with that of the commonly used diagnostic signs including the chest *x*-ray. Patients not on beta-blockade treatment could be separated into three distinct arterial pressure responses detectable at the bedside which corresponded well to three statistically different groups with regard to left ventricular ejection fraction (0·29±0·11, 0·48±0·15, 0·69±0·11) and left ventricular end-diastolic pressure (38±5 mmHg, 24±10 mmHg, 14±5 mmHg) at subsequent cardiac catheterisation. In patients not on beta-blockade it was shown for the first time that (1) the height of the systolic arterial pressure overshoot was directly related to left ventricular ejection fraction and inversely related to left ventricular end-diastolic pressure, and that (2) the bedside sphygmomanometrically determined arterial pressure response during Valsalva manoeuvre provided a semiquantitative estimate of left ventricular function and was unsurpassed in its ability to do so by any of the standard diagnostic signs including the chest *x*-ray film.

Although Weber and not Valsalva first described the circulatory effects of airway straining,[1] the clinical manoeuvre consisting of sustained forced expiratory effort against an obstructed airway (closed glottis or column of mercury) bears the name "Valsalva" after its description by this man almost two hundred years ago.[2] The normal arterial blood pressure response to the Valsalva manoeuvre is an initial rise associated with the onset of straining (phase 1), followed by a sharp fall to below baseline levels as the straining is maintained (phase 2). Release of strain (phase 3) is followed in the normal subject by a distinct overshoot of the arterial pressure (phase 4) creating a typical sinusoidal response (Fig. 1a). Hamilton first observed that during the straining phase of the Valsalva manoeuvre arterial pressure remained unchanged in patients with congestive heart failure instead of decreasing precipitously as in the normal.[3] Though the bedside application of this manoeuvre for the detection of congestive heart failure was advocated over 20 years ago[4–6] haemodynamic studies demonstrating its relative sensitivity and specificity in this regard have been inadequate and perhaps are responsible for the conspicuous absence of this manoeuvre in most textbooks of physical diagnosis.[7–9]

Recent studies dealing with the usefulness of physical signs in detection of congestive heart failure depend upon a rise in left ventricular end-diastolic pressure obtained during left heart catheterisation to establish both the diagnosis and the degree of left ventricular dysfunction.[10 11] The concomitant use of ejection indices of myocardial performance such as ejection fraction are considered by many to help substantially in establishing the diagnosis and degree of left ventricular failure.[12–14]

The present report assessed the clinical value of the application of the Valsalva manoeuvre in the

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detection of left ventricular dysfunction by investigating (a) the diagnostic accuracy of bedside sphygmomanometric detection of the arterial pressure response when compared with central aortic pressure tracings obtained during cardiac catheterisation; (b) the previously unreported relation between the systemic arterial pressure response and left ventricular ejection fraction; (c) the previously unreported relation between systemic arterial pressure response and left ventricular end-diastolic pressure; and (d) the value of this manoeuvre when applied prospectively at the bedside for the clinical detection of left ventricular dysfunction compared with the routine physical diagnostic signs, including chest radiography.

Patients and methods

Thirty-seven consecutive patients undergoing left heart catheterisation for evaluation of chest pain and/or dyspnoea were chosen for study. Patients with mitral or aortic stenosis, constrictive pericarditis, coarctation of the aorta, and atrial septal defect were excluded by study design since previously reported data[15–17] suggest an abnormal response during the Valsalva manoeuvre in such individuals, possibly related to haemodynamic indices other than congestive heart failure itself. Diagnoses in this group of patients included six normal individuals, 25 with coronary artery disease, one with mitral valve regurgitation, three with aortic valve regurgitation and two with primary myocardial disease with associated mitral regurgitation.

All patients were examined by three physicians (an internist and/or cardiologist, cardiology fellow, and medical resident) within 12 hours before the time of cardiac catheterisation. To maximise the sensitivity of the routine physical signs, their presence during the examination by any of the above physicians was considered diagnostic in the case of that individual patient. The bedside performance of the Valsalva manoeuvre with sphygmomanometric detection of the arterial pressure response was done by a single physician as originally described by Knowles and Gorlin.[6] Briefly, the patient was instructed how to perform the Valsalva manoeuvre. The systolic blood pressure was routinely obtained while the patient was quietly breathing with normal tidal volumes in the supine position. The cuff pressure was then raised 15 mmHg above the systolic pressure and the patient was asked to perform the Valsalva manoeuvre at the end of a normal inspiratory effort. The effectiveness of the procedure was assessed by noting if the patient had developed a florid face, distended neck veins, and increased abdominal muscle wall tone. After 10 seconds the patient was instructed to relax his abdomen and resume normal quiet breathing. During the strain phase of the Valsalva manoeuvre and for 15 seconds afterwards the cuff pressure was held inflated 15 mmHg above the previously determined systolic pressure while Korotkoff sounds were sought by auscultation over the brachial artery. Responses were characterised as either (a) sinusoidal, (b) absent overshoot, or (c) square wave (Fig. 1). Auscultation with cuff pressure held inflated 15 mmHg above the previously determined systolic pressure disclosed Korotkoff sounds at the initiation of the straining phase (phase 1) in all three types of pressure responses. In both the sinusoidal and absent overshoot responses these sounds were not perceived during continued later straining. In the square wave response, however, the Korotkoff sounds were heard at this level of systolic pressure for the entire duration of the straining phase. Only those patients with a sinusoidal response had return of Korotkoff sounds at this maintained cuff pressure approximately three to 10 seconds (phase 4 or overshoot) after relaxation (phase 3).

During cardiac catheterisation but before injection of any contrast material, the Valsalva manoeuvre was repeated with the patient sustaining a minimal effective intraoral pressure of 40 mmHg for 10 seconds. The arterial pressure response in the ascending aorta was recorded at a paper speed of 25 mm/s. These responses were analysed with special attention to the height of phases 1 and 4 as well as the presence or absence of a decrease in pulse pressure during phase 2.

End-diastolic pressure was identified as the pressure in the left ventricular chamber after atrial systole (post "a" wave) and before ventricular contraction. In patients in whom no "a" wave existed, end-diastolic pressure was measured 0·05 s after the onset of the QRS complex.[18] Mean pulmonary capillary wedge pressure ($\bar{P}_c$) was substituted for left ventricular end-diastolic pressure in all three cases with chronic mitral regurgitation, since symptomatology and *x*-ray findings more often reflect this left ventricular filling pressure in these individuals. In all patients left ventricular end-diastolic pressure or $\bar{P}_c$ was obtained from a series of representative cardiac cycles.

Left ventricular ejection fraction was determined by the single plane area length method[19] as well as by Simpson's rule.[20] In all cases agreement between the two methods was excellent. The absolute values reported are those obtained by the area-length method.

Patients on and off beta-blockade treatment were analysed separately to exclude the effects of propranolol on left ventricular haemodynamics and/or baroreceptor mediated neural reflex arc.

Significant differences between mean left ventricular end-diastolic pressures ($\bar{P}c$) and ejection fractions of the various systemic arterial pressure groups were sought using the two-tailed Student's t test. Pearson "r" correlation coefficients between certain of the variables were calculated by the raw score method and linear regression equations derived by previously well-described methods.[21] Differences between correlation coefficients were tested for significance by use of the Fisher transformation "z".[22]

Where available, routine posteroanterior and lateral chest *x*-ray films taken within 48 hours of the time of cardiac catheterisation were read independently by two cardiovascular radiologists and graded for the presence of congestive heart failure without knowledge of the catheterisation findings. The grading system was as follows: 1, normal pulmonary blood flow with greater flow to the bases than the apices; 2, equal pulmonary blood flow distribution to the upper and lower lobes; 3, cephalisation of pulmonary blood flow with upper lobe greater than lower lobe flow; 4, alveolar air space oedema. Cardiomegaly was defined as a cardiothoracic ratio > 0·50.

Comparisons among the various physical diagnostic signs in the detection of left ventricular dysfunction were made according to the following definitions:

True positive: physical sign present, LVEDP $\geqslant 15$ mmHg[11]

True negative: physical sign absent, LVEDP < 15 mmHg

False positive: physical sign present, LVEDP < 15 mmHg

False negative: physical sign absent, LVEDP $\geqslant 15$ mmHg

Sensitivity: true positives/total patients with LVEDP $\geqslant 15$ mmHg

Specificity: true negatives/total patients with LVEDP < 15 mmHg

PV pos (predictive value of presence of a physical sign): true positives/total number in whom physical sign is present

PV neg (predictive value of absence of a physical sign); true negatives/total number in whom physical sign is absent

PE (predictive error): false negatives/total number in whom physical sign is absent

RR (relative risk): PV pos/PE.

Results

(A) CATHETERISATION FINDINGS

The three patterns of arterial pressure response during the Valsalva manoeuvre recorded at the time of cardiac catheterisation are shown in Fig. 1.

Of 16 patients not on propranolol therapy, the "sinusoidal" response (Fig. 1A) was observed in seven patients with a mean left ventricular ejection fraction of 0·69 ± 0·11 and a mean left ventricular end-diastolic pressure of 14 ± 5 mmHg. An "absent overshoot" of arterial systolic pressure < 15 mmHg above baseline,[5] was seen in four patients with a mean left ventricular ejection fraction of 0·48 ± 0·15 and mean left ventricular end-diastolic pressure of 24 ± 10 mmHg. A "square wave" arterial pressure response (Fig. 1C) was recorded in five patients with a mean left ventricular ejection fraction of 0·29 ± 0·11 and mean left ventricular end-diastolic pressure of 38 ± 5 mmHg. Left ventricular ejection fraction means were significantly different for the square wave vs absent overshoot response ($p < 0{\cdot}01$), square wave vs sinusoidal response ($p < 0{\cdot}001$), and absent overshoot vs sinusoidal response ($p < 0{\cdot}005$). Left ventricular end-diastolic pressure means were significantly different for the square wave vs

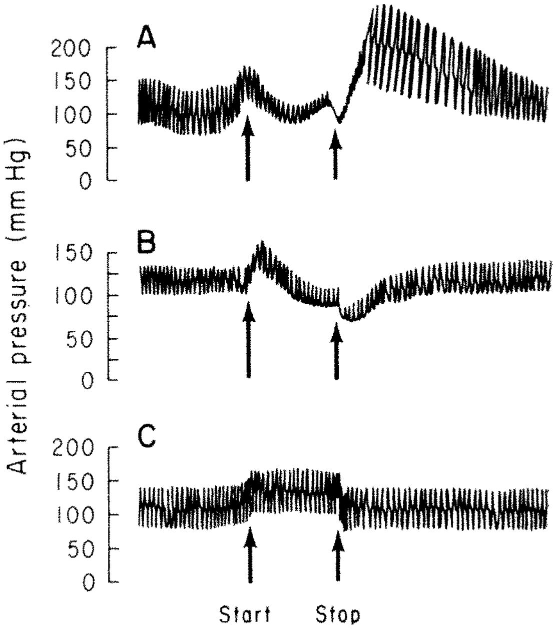

Fig. 1 *Arterial pressure responses during Valsalva manoeuvre.* (A) *Sinusoidal arterial pressure response;* (B) *absent overshoot arterial pressure response;* (C) *square wave arterial pressure response.*

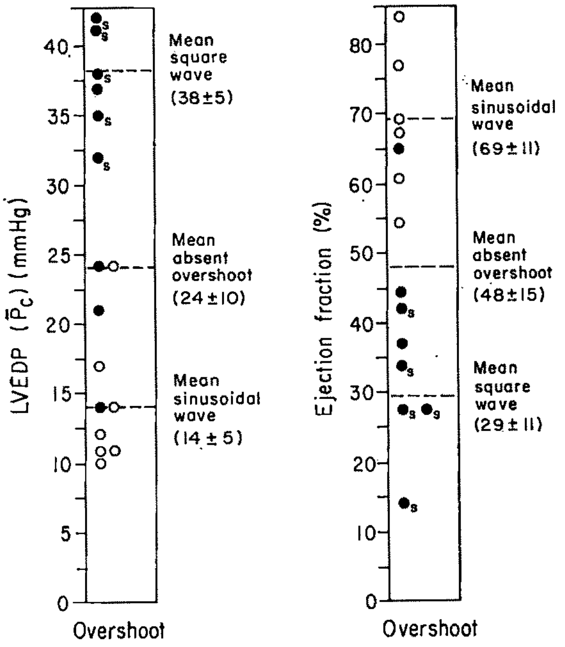

Fig. 2 *Left ventricular ejection fraction and left ventricular end-diastolic pressure (LVEF and LVEDP) vs arterial pressure response during the Valsalva manoeuvre.* ○, *sinusoidal arterial pressure response;* ●, *absent overshoot arterial pressure response;* ●s, *square wave arterial pressure response.*

sinusoidal response ($p<0.001$) and absent overshoot vs sinusoidal response ($p<0.05$) (Fig. 2).

In a similar group of patients it has been previously shown that airway pressure during straining approximates closely to intraoesophageal pressure[16] and that the latter during initial straining approximates to the magnitude of the early systolic arterial pressure rise (phase 1).[23] In our study there was no significant correlation between the degree of systolic arterial pressure initially generated during the Valsalva manoeuvre (magnitude of phase 1) and the height of the overshoot (magnitude of phase 4), provided a sufficient increase in intrathoracic pressure had taken place (intraoral pressure >40 mmHg for 10 seconds). The height of the pressure overshoot was, however, related directly to the magnitude of the left ventricular ejection fraction ($r=0.72$) (Fig. 3) and inversely to the magnitude of the left ventricular end-diastolic pressure ($r=-0.79$) (Fig. 4).

In 21 patients receiving propranolol no significant correlation between left ventricular ejection fraction or left ventricular end-diastolic pressure and the height of the systolic arterial pressure overshoot was found (Fig. 5). Though propranolol did appear to decrease the level of overshoot, an overshoot >15 mmHg was always associated with a left ventricular ejection fraction >0·50 and left ventricular end-diastolic pressure <24 mmHg in all patients studied regardless of the aetiology of

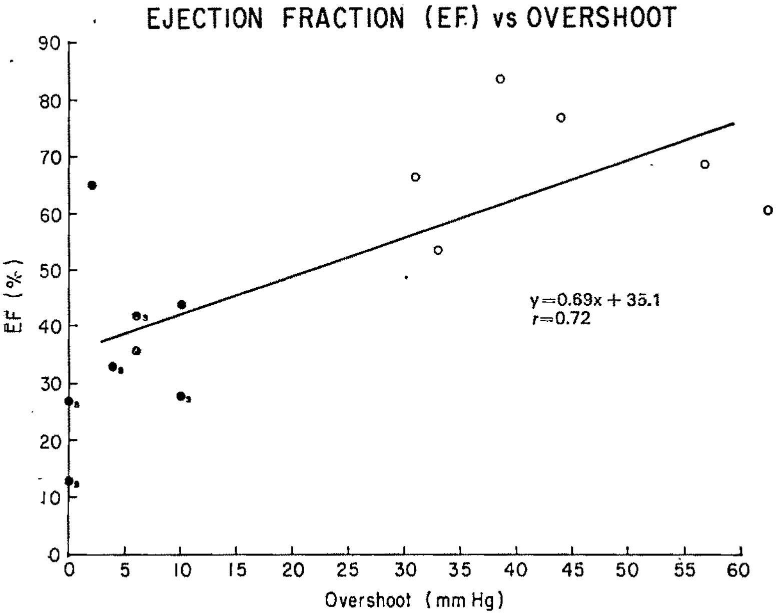

Fig. 3 *LVEF vs height of systolic arterial pressure overshoot.* ○, *sinusoidal arteria response;* ●, *absent overshoot arterial pressure response;* ●s, *square wave arterial pressure response.*

their heart disease and the presence or absence of beta-blockade treatment.

No patient in this series suffered angina pectoris, syncope, or ST-T segment alterations during the Valsalva manoeuvre.

(B) BEDSIDE VALSALVA FINDINGS

The sphygmomanometrically observed arterial pressure response during the Valsalva manoeuvre accurately predicted the response recorded at catheterisation in (7/7), (3/4), and (4/5) patients with the sinusoidal, absent overshoot and square wave responses, respectively. A single case of absent overshoot response at catheterisation was misclassified clinically as sinusoidal. Similarly a case with square wave arterial pressure pattern

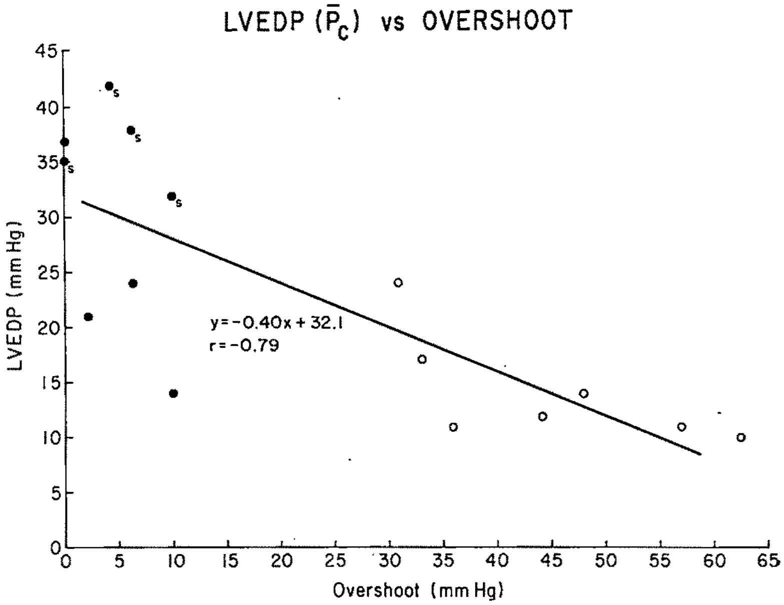

Fig. 4 *LVEDP vs height of systolic arterial pressure overshoot.* ○, *sinusoidal arterial pressure response;* ●, *absent overshoot arterial pressure response;* ●s, *square wave arterial pressure response.*

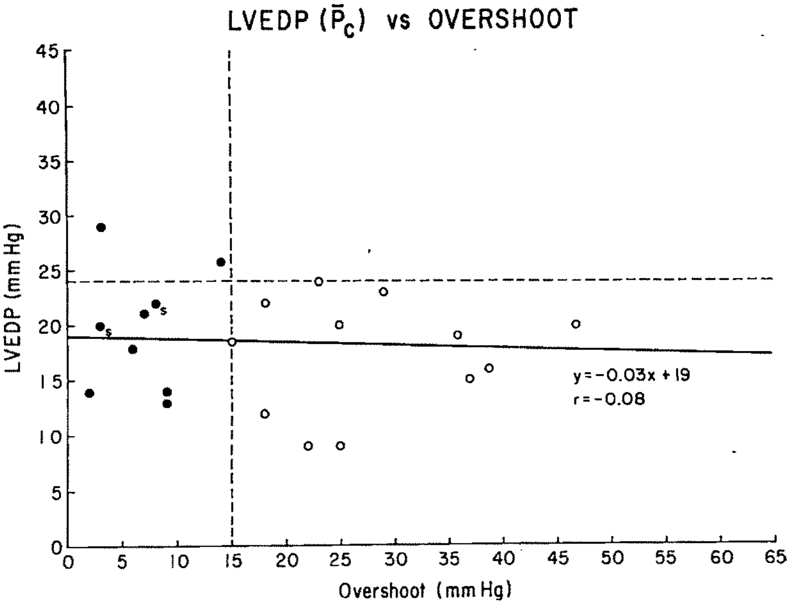

Fig. 5 *LVEDP vs height of systolic arterial pressure overshoot (patients on propranolol).* ○, *sinusoidal arterial pressure response;* ●, *absent overshoot arterial pressure response;* ●s, *square wave arterial pressure response.*

was clinically diagnosed as absent overshoot response.

Râles (20%, 5/25), ventricular gallop sounds (S_3G) (16%, 4/25), hepatojugular reflux (20%, 5/25), jugular venous distension (20%, 5/25), and peripheral oedema (8%, 2/25) were extremely insensitive indicators of raised left ventricular end-diastolic pressure ($\bar{P}_c$) (Fig. 6). An atrial gallop sound (S_4G), while sensitive (68%, 17/25), suffered from relative lack of specificity (50%, 6/12) in this regard (Table).

Fig. 6 also shows the data from posteroanterior and lateral chest radiography in this group of patients. Five of six patients with either cephalisation of pulmonary blood flow or alveolar air space oedema also had cardiomegaly. Four of six of these patients possessed square wave arterial pressure responses during the Valsalva manoeuvre.

No patient in this series had angina pectoris or syncope during the bedside performance of the Valsalva manoeuvre. Subsequent to analysis of these data, 25 additional patients with documented coronary artery disease and stable angina pectoris, who underwent the bedside Valsalva manoeuvre as previously described, had no development of chest pain during its execution.

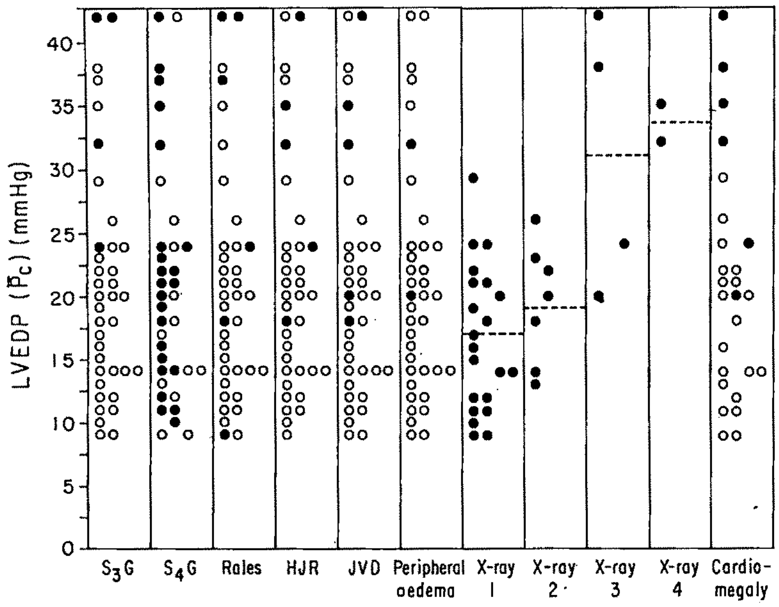

Fig. 6 *Physical examination and x-ray findings in patients with various LVEDPs; symbols in corresponding positions in various columns relate to same individual.* ●, *presence of physical sign or x-ray finding;* ○, *absence of physical sign or x-ray finding.*

Table *Physical and radiological findings in left ventricular dysfunction*

Sign	*True+*	*True—*	*False+*	*False—*	*Sens*	*Spec*	*PVpos*	*PVneg*	*RR*
S_3G	4	12	0	21	16 (31)	100 (95)	100	36	1·6
S_4G	17	6	6	8	68	50	74	43	1·3
Râles	5	11	1	20	20 (13)	92 (91)	83	35	1·3
HJR	5	12	0	20	20 (17)	100 (91)	100	38	1·6
JVD	5	12	0	20	20 (10)	100 (97)	100	38	1·6
Peripheral oedema	2	12	0	23	8 (10)	100 (93)	100	34	1·5
Non-sinusoidal sphygmomanometer, no propranolol	8	6	0	2	80	100	100	75	4·0
Chest *x*-ray Class 2, 3, 4 pulm flow	12	9	2	11	50	82	85	45	1·5
Chest *x*-ray cardiomegaly	6	9	0	11	35 (62)	100 (67)	100	45	1·8

( ) data reproduced from Harlan *et al.*[11] See Methods section of text for correlation definitions.

Discussion

The Valsalva manoeuvre is generally divided by most cardiac physiologists into four more or less well-defined phases: phase 1—onset of straining with its associated arterial pressure rise; phase 2—straining; phase 3—release of strain; and phase 4—arterial pressure overshoot (Fig. 1A). Studies in man using the pressure-gradient technique have shown that in normal subjects the arterial pressure response during the four phases of Valsalva is the result of an acute increase in intrathoracic pressure (phase 1); decreased stroke volume secondary to decreased venous return and compensatory rise in peripheral vascular resistance with narrowing of pulse pressure (phase 2); an acute decrease in the level of intrathoracic pressure (phase 3); and a distinct increase in stroke volume over control level with concomitant decrease in peripheral vascular resistance (phase 4).[24] M-mode echocardiographic studies have shown reduced left atrial size,[25] and reduced left ventricular internal dimension in systole and diastole with a resultant fall in stroke volume during phase 2.[25 26] Angiographic methods have also shown decreased left ventricular end-diastolic volume and stroke volume during phase 2.[27] Echocardiography has failed, however, to document an increase in stroke volume during phase 4 above that of control levels.[25] Phases 2 and 4 are associated with a relative tachycardia and bradycardia, respectively.

Experimental work in the dog[28 29] has yielded results consistent with the hypothesis that the normally present overshoot (phase 4) is the result of reflex sympathetic activity engendered by the hypotension present in several circulatory baroreceptors, including the carotid sinuses during the period that venous return is impaired.[30] Arterial baroreceptor hypotension during phase 2 causes decreased carotid sinus nerve stimulation with enhanced alpha and beta sympathetic efferent traffic via the cardiac sympathetic nerves[31 32] resulting in tachycardia (beta), enhanced contractility (beta), and increased peripheral vascular resistance (alpha).[33 34]

Physiological events are different in patients with left ventricular dysfunction and the square wave arterial pressure response during the Valsalva manoeuvre. Stroke volume increases initially (phase 1) and then continues to remain raised over control levels during the remainder of the strain period (phase 2). Immediately before phase 3 there is a fall in stroke volume and a rise in peripheral vascular resistance.[35] The relative tachycardia and bradycardia of phases 2 and 4, respectively, are also conspicuously absent in this group of patients.[26]

Previous studies in people dealing with the value of the Valsalva manoeuvre in the detection of congestive heart failure have been haemodynamically limited and have not dealt with the question of relative sensitivity and specificity when compared with the other physical diagnostic signs. Though Gorlin presented right heart catheterisation data in 78 patients, there were only seven presumed normal controls and six patients with presumed coronary artery disease in his series.[16] In addition perhaps 42 of 78 possessed cardiac lesions which, independent of associated congestive heart failure, might have been responsible for the abnormal circulatory response noted. As detailed previously, data from these patient groups were not included in our analysis. Moreover, of the remaining 36 patients in Gorlin's series, 13 had recordings of only the right atrial pressure as an estimate of the degree of "heart failure". In two other reports of haemodynamic studies using right heart catheterisation techniques, the arterial response to the Valsalva manoeuvre could be attributed to the presence or absence of congestive heart failure in only 17 patients[36] and 10 patients.[23]

Results of this study suggest for the first time that (1) the height of the arterial overshoot may be directly related to the magnitude of the left ventricular ejection fraction and inversely related to ($\bar{P}_e$) left ventricular end-diastolic pressure and (2) the clinical value of the bedside sphygmomanometrically determined arterial pressure response in assessing the degree of left ventricular dysfunction in patients not on propranolol is unsurpassed by any of the standard diagnostic signs including the chest *x*-ray film. The Table summarises the sensitivity, specificity, positive and negative predictive accuracies, and relative risk for left ventricular dysfunction of the various diagnostic signs based upon a left ventricular end-diastolic pressure ($\bar{P}_e$) $\geqslant 15$ mmHg[11] at rest. Excellent agreement was noted between our series and that of Harlan and associates[11] regarding the ability of the standard physical signs to indicate left ventricular failure. Thus the superiority of the bedside Valsalva manoeuvre for detecting left ventricular failure in our study was not merely secondary to poor clinical acumen by our physicians in the recognition of the conventional signs on physical examination.

The ability to separate patients not on beta-blockade treatment into three systolic arterial pressure response groups during Valsalva at the bedside was confirmed, and it was determined for the first time that such clinically detectable responses corresponded to three statistically different groups of individuals with regard to left ventricular ejection fraction (0·29 ±0·11, 0·48 ±0·15, 0·69 ±0·11) and left ventricular end-diastolic pressure (38 ±5 mmHg, 24 ±10 mmHg, 14 ±5 mmHg).

Our clinical data derived from patients on propranolol treatment suggest that beta-adrenergic antagonists may alter the relation between left ventricular end-diastolic pressure (or left ventricular ejection fraction) and the height of the phase 4 overshoot (Fig. 5). Though a significant percentage of patients in this study was receiving propranolol, an overshoot greater than 15 mmHg, regardless of treatment was always associated with a left ventricular ejection fraction $>0·50$ and left ventricular end-diastolic pressure <25 mmHg. Thus the absence of a clinically detectable overshoot (<15 mmHg) is non-diagnostic in patients on propranolol, but the presence of such an arterial overshoot excludes the possibility of moderate to severe left ventricular dysfunction.

Experimentally, norepinephrine (alpha-agonist) infusion will diminish the extent of the arterial overshoot in normal subjects.[29] Recent clinical studies disclose increased plasma concentrations of norepinephrine in patients with congestive heart failure.[37] Thus the absent overshoot response during Valsalva manoeuvre in patients with raised left ventricular end-diastolic pressure and diminished left ventricular ejection fraction may be related to plasma norepinephrine levels. Moreover, the direct and inverse correlations shown between the height of the systolic arterial pressure overshoot and left ventricular ejection fraction and left ventricular end-diastolic pressure respectively, may be a function of plasma norepinephrine concentrations which are proportional to the degree of congestive heart failure.[37] The almost immediate altered response of certain patients during the Valsalva manoeuvre to acute postural changes[16] suggests, however, that the absent overshoot is the result of peripheral vasoconstriction leading to a relative expansion of pulmonary blood volume[29] and pulmonary extravascular water volume,[38] the latter being related to hydrostatic pulmonary capillary wedge pressure by the Starling hypothesis for capillary filtration.

Syncope while in the supine position, at least in normal subjects at rest, is rare during the performance of the Valsalva manoeuvre. In the presence of respiratory alkalosis, however, with its associated cerebral vasoconstriction, the decreased cardiac output and mean aortic blood pressure which occurs during late phase 2 and phase 3[24] may be sufficient to produce syncope even while supine in approximately 50 per cent of normal subjects.[39] In our experience with over 60 patients at rest, we have not encountered a single syncopal episode. This may be attributable to the purposeful time limitation of the straining phase in our patients by the accompanying physician. In addition the greatest risk for respiratory alkalosis during basal conditions would be present in those with the most severe left ventricular dysfunction. Such patients showed a square wave arterial pressure response during Valsalva, raising and not lowering both cardiac output and mean aortic blood pressure during the period of strain (phase 2).[35]

Although some have questioned the safety of the Valsalva manoeuvre in patients with coronary artery disease,[40] others have reported no adverse clinical effects and even occasional relief of angina pectoris when performing this manoeuvre.[41] The effects of this manoeuvre upon myocardial oxygen consumption as well as coronary arterial blood flow will vary with the type of arterial pressure response considered. In this regard, at least three of Levine *et al.*'s[41] six patients who experienced symptomatic relief from their anginal attacks during the Valsalva manoeuvre possessed normal sinusoidal arterial pressure responses.

Although conditions other than left ventricular dysfunction such as prerenal azotaemia or haemorrhage (decreased intravascular volume),[28] and idiopathic orthostatic hypotension[42] may also cause an absent overshoot arterial pressure response, these conditions can usually be differentiated from failure on the basis of the clinical history.

Until further data are available, we must conclude that this procedure may not be completely innocuous in patients with acute coronary heart disease both because of haemodynamic considerations as regards coronary artery blood flow and possibly because of the associated increases in vagal tone which may be arrhythmogenic under such circumstances.[43] [44] In patients with coronary artery disease, stable angina pectoris, and a wide range of left ventricular ejection fractions (0·21 to 0·71) and end-diastolic pressures (10 to 42 mmHg), however, it has been our experience that performance of this manoeuvre by the patient in the presence of a physician is simple, safe, and can be readily accomplished by almost all individuals with the proper instruction. Moreover, bedside sphygmomanometric assessment of the arterial pressure response during Valsalva far surpasses all other routinely available bedside diagnostic signs in the detection of left ventricular dysfunction and provides in certain subjects a reliable estimation of its severity.

References

1 Derbes VJ, Kerr A Jr. Valsalva's maneuver and Weber's experiment. *N Engl J Med* 1955; **253:** 822–3.

2 Valsalva AM. *De aure humana tractatus* Utrecht: G. Vande Water, 1707: 84.

3 Hamilton WF, Woodbury RA, Harper HT Jr. Arterial, cerebrospinal and venous pressures in man during cough and strain. *Am J Physiol* 1944; **141:** 42–50.

4 Sharpey-Schafer FP. Effects of Valsalva's manoeuvre on the normal and failing circulation. *Br Med J* 1955; **1:** 693–5.

5 Knowles JH, Gorlin R, Storey CF. Clinical test for pulmonary congestion with use of the Valsalva maneuver. *JAMA* 1956; **160:** 44–8.

6 Irvin CW Jr. Valsalva maneuver as a diagnostic aid. *JAMA* 1959; **170:** 787–91.

7 Hochstein E, Rubin AL. *Physical diagnosis* New York: McGraw Hill, 1964.

8 DeGowin EL, DeGowin RL. *Bedside diagnostic examination.* 2nd ed. New York: Macmillan, 1969.

9 Judge RD, Zuidema GD. *Methods of clinical examination.* 3rd ed. Boston: Little Brown, 1974.

10 Riley CP, Russell RO Jr, Rackley CE. Left ventricular gallop sound and acute myocardial infarction. *Am Heart J* 1973; **86:** 598–602.

11 Harlan WR, Oberman A, Grimm R, Rosati RA. Chronic congestive heart failure in coronary artery disease; clinical criteria. *Ann Intern Med* 1977; **86:** 133–8.

12 Braunwald E, Ross J Jr. The ventricular end-diastolic pressure: appraisal of its value in the recognition of ventricular failure in man. *Am J Med* 1963; **34:** 147–50.

13 Dodge HT, Baxley WA. Hemodynamic aspects of heart failure. *Am J Cardiol* 1968; **22:** 24–34.

14 Rackley CE, Hood WP Jr, Rolett EL, Young DT. Left ventricular end-diastolic pressure in chronic heart disease. *Am J Med* 1970; **48:** 310–9.

15 Goldberg H, Elisberg EI, Katz LN. The effects of the Valsalva-like maneuver upon the circulation in normal individuals and patients with mitral stenosis. *Circulation* 1952; **5:** 38–47.

16 Gorlin R, Knowles JH, Storey CF. The Valsalva maneuver as a test of cardiac function. *Am J Med* 1957; **22:** 197–212.

17 Hancock EW, Oliver GC, Swanson MJ, Hultgren HN. Valsalva's maneuver in atrial septal defect. *Am Heart J* 1963; **65:** 50–8.

18 Braunwald E, Fishman AP, Cournand A. Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. *Circ Res* 1956; **4:** 100–7.

19 Rackley CE. Quantitative evaluation of left ventricular function by radiographic techniques. *Circulation* 1976; **54:** 862–79.

20 Chapman CB, Baker O, Reynolds J, Bonte F. Use of biplane cinefluorography for measurement of ventricular volume. *Circulation* 1958. **18:** 1105–17.

21 Runyon RP, Haber A. *Fundamentals of behavioral statistics.* 2nd ed. Reading, Massachusetts: Addison-Wesley, 1971: 94–128.

22 Fisher RA. On the "probable error" of a coefficient of correlation deduced from a small sample. *Metron* 1921; **14:** 3–32.

23 Stone DJ, Lyon AF, Teirstein AS. A reappraisal of the circulatory effects of the Valsalva maneuver. *Am J Med* 1965; **39:** 923–33.

24 Greenfield JC Jr, Cox RL, Hernandez RR, Thomas C, Schoonmaker FW. Pressure-flow studies in man during the Valsalva maneuver with observations on the mechanical properties of the ascending aorta. *Circulation* 1967; **35:** 653–61.

25 Robertson D, Stevens RM, Friesinger GC, Oates JA. The effect of the Valsalva maneuver on echocardiographic dimensions in man. *Circulation* 1977; **55:** 596–602.

26 Parisi AF, Harrington JJ, Askenazi J, Pratt RC, McIntyre KM. Echocardiographic evaluation of the Valsalva maneuver in healthy subjects and patients with and without heart failure. *Circulation* 1976; **54:** 921–7.

27 Brooker JZ, Alderman EL, Harrison DC. Alterations in left ventricular volume induced by Valsalva manoeuvre. *Br Heart J* 1974; **36:** 713–8.

28 Sarnoff SJ, Hardenbergh E, Whittenberger JL. Mechanism of the arterial pressure response to the Valsalva test; the basis for its use as an indicator of the intactness of the sympathetic outflow. *Am J Physiol* 1948; **154:** 316–27.

29 Price HL, Connor EH. Certain aspects of the hemodynamic response to the Valsalva maneuver. *J Appl Physiol* 1953; **5:** 449–56.

30 Linden RJ. Function of cardiac receptors. *Circulation* 1973; **48:** 463–80.

31 Delius W, Hagbarth KE, Hongell A, Wallin BG. Manoeuvres affecting sympathetic outflow in human muscle nerves. *Acta Physiol Scand* 1972; **84:** 82–94.

32 Wallin BG, Delius W, Hagbarth KE. Comparison of sympathetic nerve activity in normotensive and hypertensive subjects. *Circ Res* 1973; **33:** 9–21.

33 Szentivanyi M, Juhász-Nagy A. The physiological role of the coronary constrictor fibres. I. The effect of the coronary vasometers on the systemic blood pressure. *Q J Exp Physiol* 1963; **48:** 93–104.

34 Feigh EO. Carotid sinus reflex control of coronary blood flow. *Circ Res* 1968; **23:** 223–37.

35 Ruskin J, Harley A, Greenfield JC Jr. Pressure-flow studies in patients having a pressor response to the Valsalva maneuver. *Circulation* 1968; **38:** 277–81.

36 Judson WE, Hatcher JD, Wilkins RW. Blood pressure responses to the Valsalva maneuver in cardiac patients with and without congestive failure. *Circulation* 1955; **11:** 889–99.

37 Thomas JA, Marks BH. Plasma norepinephrine in congestive heart failure. *Am J Cardiol* 1978; **41:** 233–43.

38 Yu PN. Lung water in congestive heart failure. *Mod Concepts Cardiovasc Dis* 1971; **40:** 27–31.

39 Klein LJ, Saltzman HA, Heyman A, Sieker HO. Syncope induced by the Valsalva maneuver. *Am J Med* 1964; **37:** 263–8.

40 Benchimol A, Wang TF, Desser KB, Gartlan JL Jr. The Valsalva maneuver and coronary arterial blood flow velocity.. *Ann Intern Med* 1972; **77:** 357–60.

41 Levine HJ, McIntyre KM, Glovsky MM. Relief of angina pectoris by Valsalva maneuver. *N Engl J Med* 1966; **275:** 487–9.

42 Ibrahim MM, Tarazi RC, Dustan HP. Orthostatic hypotension; mechanisms and management. *Am Heart J* 1975; **90:** 513–20.

43 McGuire J, Green RS, Hauerstein V, *et al.* Bed pan deaths. *Am Pract Digest Treatment* 1950; **1:** 23–8.

44 Schartum S. Ventricular arrest caused by the Valsalva maneuver in a patient with Adams-Stokes attacks accompanying defecation. *Acta Med Scand* 1968; **184:** 65–8.

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Management of ventricular septal rupture in acute myocardial infarction

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SUMMARY Four patients with rupture of the interventricular septum after myocardial infarction are described. This condition carries a grave prognosis. Surgical repair of the septum is almost always urgently required if the left-to-right shunt is large (QP/QS>3). Results are better if surgery can be deferred for six weeks to allow the infarcted area to heal and the tissues to become firmer. This delay may be achieved by using a combination of agents to reduce afterload and to exert a positive inotropic effect. The timing of surgical intervention was an important factor in the survival of three of the four patients.

Ventricular septal defect after acute myocardial infarction was first described by Latham in 1846.[1] Rupture of the ventricular septum occurs within the first few days of myocardial infarction when it is poorly tolerated. It accounts for approximately 0·5 to 1·5 per cent of all deaths from acute myocardial infarction. In the absence of surgical intervention the condition is almost invariably fatal.[2] Sanders *et al.*[3] found that 54 per cent died within the first week of perforation and only 13 per cent survived two months or longer.

The development of cardiogenic shock and severe left ventricular failure are the most important factors in deciding the outcome. Both are determined by the size of the infarct and the magnitude of the left-to-right shunt.[4] Repair of ventricular septal rupture was first attempted in 1956.[5] The optimal time for this is still uncertain; the results of early intervention are poor.[6–9]

This report describes successful repair in three out of four consecutive patients. The time at which operation was undertaken depended on early measurement of the size of the shunt and continuous clinical assessment of the patient.

Case reports

CASE 1

A 54-year-old housewife was admitted with an acute inferior infarction (Table 1). She was in sinus rhythm (rate 90/min) and her blood pressure was 150/105 mmHg. No murmurs were noted. Within 48 hours of admission, complete heart block developed, preceded by sinus bradycardia and first and second degree atrioventricular block. The ventricular rate fell to 50/min and the blood pressure to 80/60 mmHg. Temporary atrioventricular sequential pacing was started. The blood pressure rose to 120/80 mmHg. Three days later sinus rhythm returned. The same day severe central chest pain recurred. The electrocardiogram showed sinus tachycardia at 120/min, with further ST segment elevation in leads II, III, and aVF. The blood pressure was 105/80 mmHg. The jugular venous pressure was raised with prominent 'a' and 'v' waves. A loud pansystolic murmur accompanied by a thrill was noted at the lower left sternal edge. A Swan-Ganz balloon tip catheter was inserted at the bedside. A large left-to-right shunt (QP/QS 4·8:1) was confirmed at ventricular level (Table 2). Systolic blood pressure had fallen to 65 mmHg. Digoxin and diuretics were started along with a dobutamine infusion. In view of the size of the shunt, persistent hypotension, and increasing congestive cardiac failure operation was carried out 10 hours after the development of the ventricular septal defect. At operation the right ventricle was greatly enlarged. The inferior surface of the heart was the site of a large haemorrhagic infarct covering most of the base and extending into the mitral annulus. The left ventricle was opened through its inferior surface using a longitudinal incision through the area of infarction parallel to the posterior descending coronary artery. The mitral apparatus and the papillary muscles appeared

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Table 1 *Clinical data*

Case No.	*Age (y)*	*Sex*	*MI*	*MI to VSD (days)*	*VSD to surgery*	*History of hypertension*	*History of MI*	*BP on admission (mmHg)*	*Conduction disturbances*	*Operation*	*Outcome*
1	54	F	Inferior	5	10 hours	Unknown	0	150/105	CHB	Repair of VSD	Alive (died 14 mths after initial admission)
2	59	M	Anteroseptal	10	40 days	Yes	0	130/80	RBBB and LAHB	Repair of VSD and aneurysmectomy	Alive
3	58	F	Anteroseptal	7	40 days	Yes	0	180/100	Transient CHB	Repair of VSD, aneurysmectomy, plication of aneurysm and SVG to RCA and Cx	Alive
4	45	M	Anteroseptal	4	26 days	Yes	0	160/105	None	Repair of VSD and plication of aneurysm	Died at operation

MI, myocardial infarction; VSD, ventricular septal defect; CHB, complete heart block; RBBB and LAHB, right bundle-branch block and left anterior hemiblock; SVG, saphenous vein graft; RCA and Cx, right coronary artery and circumflex.

normal. There was a large ventricular septal defect (2·5 cm diameter) in the middle third of the septum close to the diaphragmatic surface. The surrounding muscle was necrotic, especially towards the base of the heart. The defect was closed with a Dacron patch applied from the left ventricle and sutured with Teflon pledgets in the right ventricle. The postoperative course was uncomplicated though mechanical respiratory support was required for three days. She remained in sinus rhythm with normal heart sounds and no systolic bruit. Digoxin was continued. On the 23rd postoperative day she was discharged, asymptomatic on moderate activity. She remained well until 14 months later when a further diaphragmatic infarction occurred. She died in cardiogenic shock. Necropsy disclosed that the patch was intact. Extensive recent and old infarcts of the inferior wall were noted, with recent occlusion of the right coronary artery and extensive disease of the left anterior descending and circumflex coronary arteries.

CASE 2

A 59-year-old company director was admitted with an acute anterior infarction. He was in sinus rhythm with a blood pressure of 130/80 mmHg. Forty-eight hours later the electrocardiogram showed bifascicular block (right bundle-branch block and left anterior hemiblock). On the tenth day after infarction a loud pansystolic murmur was noted at the lower left sternal edge accompanied by a thrill. He had not experienced any further chest discomfort.

Cardiac catheterisation with a Swan-Ganz

Table 2 *Haemodynamic data*

Case No.	1		2				3				4			
Study			*First*		*Second*		*First*		*Second*		*First*		*Final*	
Position	*Pressure mmHg S D*	O_2*% sat*	*Pressure mmHg S D*	O_2*% sat*	*Pressure mmHg S D*	O_2*% sat*	*Pressure mmHg S D*	O_2*% sat*	*Pressure mmHg S D*	O_2*% sat*	*Pressure mmHg S D*	O_2*% sat*	*Pressure mmHg S D*	O_2*% s at*
PAW	(20)		(15)		(19)		(21)		(27)		(20)			
PA	37 20	82	27 13	64	44 17	77	64 26	69	65 28	84	42 22	78	48 23	77
	(28)		(20)		(30)		(45)		(45)		(31)		(35)	
RV	38 12	86	27 8	80	45 7	90	64 12	70	65 10	89	48 6	79	50 23	78
RA	(8)	44	(6)	59	(4)	66	(10)	46	(6)	62	(4)	48	(23)	52
Femoral artery/ aorta	65 40	92	90 60	94	100 62	97	111 65	86	120 66	96	90 70	93	95 62	94
LV					101 28	98			120 34	98			94 27	94
QP/QS	4·8		1·2		1·6		2·4		2·6		3·0		2·9*	

PAW, pulmonary artery wedge; PA, pulmonary artery; RV, right ventricle; RA, right atrium; LV, left ventricle; QP/QS, ratio of pulmonary to systemic flow; S, systolic; D, diastolic; ( ), mean.

*Patient had tricuspid regurgitation; QP calculated using mixed venous sample not shown.

balloon tip catheter was performed. A small left-to-right shunt at the ventricular level (QP/QS 1·2:1) was found (Table 2). Treatment with digoxin, diuretics, and labetalol was started. Over the next few days he developed frequent ventricular ectopics which were controlled by oral mexiletine 200 mg tid. Subsequently a gradual increase in the pulmonary vascularity on chest *x*-ray films was noted and the heart became larger, suggesting some increase in the size of the left-to-right shunt. Labetalol was stopped. The heart rate remained at 95/min and the systolic blood pressure at 90 mmHg. Two weeks after ventricular septal rupture, a mid-diastolic murmur became audible along with third and fourth heart sounds at the apex. Six weeks from the onset of symptoms he underwent cardiac catheterisation and coronary arteriography (Table 2). The shunt was now larger (QP/QS 1·6:1). The left ventricular end-diastolic pressure was conspicuously raised particularly after angiography. There was a large akinetic area involving the anterior wall and apex of the left ventricle. The septum appeared aneurysmal and the septal defect appeared to consist of multiple holes. There was total proximal obstruction of the left anterior descending coronary artery. The right coronary artery showed some narrowing, but this was less than 50 per cent of the lumen. The circumflex vessel was dominant and was normal. Fifty days after the infarction, that is 40 days after the development of septal rupture, surgical repair was undertaken. The right ventricle and pulmonary artery were tense and enlarged. The left ventricle was opened through the large anterior wall aneurysm, most of which was excised. The aneurysm and scar tissue extended into the ventricular septum. The ventricular septal defect was situated anteriorly in the middle third of the septum, and was approximately 2 cm in diameter and fenestrated. It was closed from the left side with a patch of knitted Dacron, and sutured in place with interrupted Prolene sutures on pledgets on the right side of the septum. After operation bifascicular block persisted. Ventricular ectopics developed seven days later. These were not controlled by mexiletine, quinidine, procainamide, or disopyramide but propranolol 160 mg orally daily was added to mexiletine 150 mg tid and a permanent sequential atrioventricular pacemaker programmed for a rate of 70/min was inserted. The ectopics were considerably diminished. He remained asymptomatic on moderate activity and went home 33 days after the operation. He has remained well and free from angina for 13 months since operation.

CASE 3

58-year-old housewife was admitted with an acute anterior infarction. She was in sinus rhythm (rate 90/min) and her blood pressure was 180/100 mmHg. Over the next 12 hours she experienced further chest pain and the ST segment in the anterior chest leads became higher. Her pain was controlled with diamorphine, sublingual isosorbide dinitrate, and propranolol. The blood pressure was 140/85 mmHg. ST segments became isolectric on the fifth day. On the seventh day she experienced further chest pain. Sinus tachycardia at 110/min was present, the blood pressure was 140/95 mmHg, and the jugular venous pressure was raised 2 to 3 cm. A loud pansystolic murmur accompanied by a thrill was noted along the lower left sternal edge. An electrocardiogram showed recurrence of ST segment elevation in anterior chest leads. A Swan-Ganz balloon catheter was inserted and a left-to-right shunt at ventricular level (QP/QS 2·4/1) was confirmed (Table 2). She was treated with digoxin and diuretics and, in an effort to reduce the afterload, oral isosorbide dinitrate 30 mg qid and labetalol 100 mg tid were given. The latter was added to prevent an excessive rise in heart rate in response to peripheral vasodilatation. The systolic blood pressure was maintained at 100 mmHg; the heart rate was 90/min. Initially she improved but over the next 24 to 48 hours the urine output fell and the plasma urea rose. A chest film showed an increase in pulmonary vascular congestion. The jugular venous pressure remained high. A dobutamine infusion (5 μg/kg per min) was started. The combination of afterload reduction and inotropic support with dobutamine resulted in increased urinary output and a fall in the plasma urea. The venous pressure became normal. Dobutamine was withdrawn and 10 days later labetalol was stopped. The systolic blood pressure remained at 90 to 100 mmHg and the heart rate at 90 to 110/min. The dobutamine infusion was restarted three weeks after septal rupture when the plasma urea again increased and urinary output decreased and once more a good response was obtained. It was stopped after three days. Except for one episode of sinus bradycardia and transitory complete heart block, sinus rhythm was retained. Six weeks from the onset of symptoms cardiac catheterisation (Table 2) showed a large ventricular septal defect and a large anteroseptal aneurysm. Coronary angiography showed triple vessel disease. The left anterior descending coronary artery had a 60 per cent stenosis near its origin. The distal vessel was of small calibre and appeared to be recanalising. There was a single localised stenosis greater than 70 per cent in both the circumflex and right coronary arteries. The distal vessels were of good calibre. At operation 40 days after the development of the ventricular septal defect, the right ventricle was moderately enlarged and was under high pressure. There were two aneurysms of the left ventricle. The smaller was to the right of the left anterior descending coronary artery, and the larger, to the left of it, extended from the upper third of the anterior wall to the apex. The left ventricle was opened through the larger aneurysm. The ventricular septal defect was situated anteriorly in the middle third of the septum and was divided by trabeculae into two parts. The overall area was about 3 cm^2. It was closed with a Teflon patch. The larger of the two aneurysms was removed and the other plicated. Saphenous vein grafts were inserted into the circumflex and right coronary arteries. Postoperatively no murmur was audible. Sinus rhythm was retained. Digoxin and diuretic therapy were continued and the patient was discharged from hospital 15 days after operation. She remained well until six months after operation when she stopped taking digoxin and diuretics and was readmitted to hospital in congestive heart failure. This responded to treatment. No murmur was noted.

CASE 4

A 45-year-old textile worker was admitted with an acute anterior infarction. On admission he was in sinus rhythm (rate 90/min) and his blood pressure was 160/105 mmHg. He had had rheumatoid arthritis for the previous four years and was being treated with prednisolone 6 mg daily. On the fourth day after the onset of symptoms a systolic murmur was noted at the lower left sternal edge. He was still in sinus rhythm at 100/min and the blood pressure was 140/90 mmHg. Propranolol 10 mg tid and quinidine 500 mg twice daily were started; prednisolone was continued. On the tenth day after admission he became acutely dyspnoeic. Hypotension and signs of biventricular failure were present. Five-hundred ml blood were removed by venesection, and digoxin, frusemide, and a dopamine infusion were started. He was transferred to our unit for further management.

Right heart catheterisation was performed with a Swan-Ganz balloon catheter and confirmed rupture of the ventricular septum with a large left-to-right shunt (QP/QS 3:1) (Table 2). After giving 5 mg isosorbide dinitrate sublingually the mean pulmonary artery wedge pressure fell. There was an increase in systemic flow, but no change in pulmonary flow and the shunt diminished (Table 3). A nitroprusside infusion of 70 µg/min was started together with oral isosorbide dinitrate 120 mg daily (Table 3). Digoxin and frusemide were continued. Over the next 48 hours the mean pulmonary artery wedge and pulmonary artery pressures fell. The arterial pressure remained unchanged (Table 3). The nitroprusside infusion was stopped three days later and replaced by labetalol 200 mg tid orally in an effort to reduce the afterload and at the same time prevent a disproportionate rise in the heart rate. Twenty-four hours later the systolic blood pressure fell to 80 mmHg and plasma urea rose. Labetalol was reduced to 100 mg orally tid and a dobutamine infusion (500 mg 12 hourly) was started. Immediate improvement in the blood pressure was noted and in the urinary output. Labetalol was stopped after a further three days. Over the next two weeks as isosorbide dinitrate and digoxin were continued with intermittent diuretics, there was *x*-ray evidence

Table 3 *Haemodynamic response to vasodilator treatment in case 4*

	On admission				*Day one*				*Day two*			
	Control		*Isosorbide dinitrate 5 mg SL*		*Control*		*Nitroprusside 70 µg/min*		*Control*		*Nitroprusside** 70 µg/min and isosorbide dinitrate 5 mg SL*	
Position	*Pressure mmHg S D*	*O$_2$% sat*	*Pressure mmHg S D*	*O$_2$% sat*	*Pressure mmHg S D*	*O$_2$% sat*	*Pressure mmHg S D*	*O$_2$% sat*	*Pressure mmHg S D*	*O$_2$% sat*	*Pressure mmHg S D*	*O$_2$% sat*
PAW	(20)		(10)		(19)		(16)		(23)		(15)	
PA	42 22	78	35 18	79	34 20	81	28 16	83	42 26	81	30 18	81
	(31)		(26)		(28)		(22)		(34)		(24)	
RA	(4)	48	(4)	55		56		62		58		62
FA/Rad A	90 70	93	92 68	94	94 69	94		96	105 70	94	100 70	94
	(79)		(79)		(82)		(80)		(85)		(85)	
Systemic flow l/min*	3·2		3·8		3·3		3·7		3·4		3·9	
Pulmonary flow l/min*	9·7		9·8		9·6		9·7		9·6		9·7	
QP/QS	3·0		2·6		2·9		2·6		2·8		2·5	

FA/Rad A, femoral artery/radial artery. Other abbreviations as in Table 2.
*Flows measured by thermodilution.
**Measurements made before oral isosorbide dinitrate had become effective.

of a gradual increase in heart size and pulmonary vascular congestion. Two further temporary infusions of dobutamine were required. Thirty days from the onset of symptoms, cardiac catheterisation and coronary angiography were performed. The left ventricle was very dilated with a large aneurysmal sac involving most of the anterolateral wall. There was a large left-to-right shunt through the ventricular septal defect. The right ventricle was dilated and there was some tricuspid regurgitation. The right ventricular end-diastolic pressure was 23 mmHg and the mean right atrial pressure was 23 mmHg. Coronary angiography showed widespread atheroma with total proximal occlusion of the left anterior descending artery and extensive disease in the right coronary artery. The circumflex vessel was non-dominant and showed some narrowing at the origin of the obtuse marginal branch. These vessels were not suitable for saphenous vein grafting.

Surgery was carried out on the same day. The left ventricle was opened through the aneurysm. A large ventricular septal defect was situated anteriorly in the middle third of the septum measuring 2 cm in diameter. The edges of the defect were ragged and surrounded by necrotic tissue. The ventricular septal defect was closed with a Dacron patch on the left ventricular side and Teflon pledgets on the right ventricular side. The left ventricular aneurysm was plicated. The mitral valve was normal. The tricuspid valve was not regurgitant. Right ventricular pressure remained high and bypass could not be discontinued despite numerous and prolonged attempts. A further plication of an akinetic area of the left ventricle was carried out. The distal third of the right ventricle was akinetic. Exploration with a finger of the right ventricle showed that there was no residual shunt, yet, despite numerous attempts the left ventricle was unable to sustain an adequate pressure and the patient died.

At necropsy severe atheroma of the coronary arteries with a recent thrombotic occlusion of the left anterior descending artery were confirmed. There was massive recent infarction of the septum and the left ventricle. A healed infarct in the territory of the obtuse marginal branch was noted. The right ventricle was dilated and showed extensive areas of fibrosis and some infarction of the distal part. The patch closure of the defect was intact.

Discussion

After acute myocardial infarction it is often difficult to distinguish between a ventricular septal defect and mitral regurgitation secondary to papillary muscle dysfunction or rupture. Rapid confirmation of the diagnosis of a ventricular septal rupture can be carried out at the bedside by right heart catheterisation using a balloon-tip flow-directed catheter. Mitral regurgitation is diagnosed by giant 'V' waves recorded in the pulmonary wedge pressure tracing. Mitral regurgitation and ventricular septal rupture rarely occur together.[10] Coronary arteriography and left ventricular angiography carried out early after the ventricular septal rupture are associated with a high morbidity and mortality.[11]

Septal rupture complicates anterior and inferior infarctions with equal frequency[4] and there is good correlation between its position and the electrocardiographic location of infarction,[11] as our patients showed.

Conduction disturbances are common. In five patients with acute inferior infarction James[12] described varying degrees of atrioventricular block before ventricular septal rupture. Vlodaver and Edwards[13] observed atrioventricular conduction disturbances in 36 per cent of 17 patients with acquired ventricular septal defects, the majority of whom had had an anterior infarction. Complete heart block occurred in two of our patients, one (case 1) with an inferior and the other (case 3) with an anterior infarction (Table 1). In case 1 atrioventricular conduction disturbance occurred before septal rupture and in case 3, transitorily, after it. One patient with anterior infarction (case 2) developed bifascicular block before septal rupture.

Post-infarction septal defects are located in the muscular part of the septum and are associated with a high incidence of left ventricular aneurysm.[14] Schlesinger *et al.*[15] found that more than 30 per cent of patients operated on for septal rupture had a ventricular aneurysm, and Hill *et al.*[16] 68 per cent. Three of our patients had ventricular aneurysms. In the remaining patient who had surgery five days after infarction (10 hours after septal rupture) there was a large necrotic area in the inferior wall but no aneurysm.

The precipitating factors in ventricular septal rupture are unknown. It has been suggested that hypertension is important.[17] Three of our four patients had this on admission and the other, while normotensive, had a history of hypertension.

Three to six months after infarction, surgical repair of a ventricular septal defect is associated with a very low mortality[9 18–20] but septal rupture usually occurs in the first week after infarction, and, with acute volume overload of both ventricles superimposed on an infarcted left ventricle, sudden clinical deterioration and progressive, refractory congestive heart failure and often cardiogenic shock mean that most patients do not survive that long. However, successful early closure has been reported within three weeks of infarction,[11 18 21–23] though only 50 per cent or less of these patients survived to leave hospital.[18 22 23] The earliest attempt at closure has been within the first 24 hours.[11] In view of the high mortality of early correction it has been suggested that closure should be delayed until four to six weeks after infarction,[9 19 21] but the optimal time is dictated by the size of the shunt determined as early as possible after septal rupture. Mundth *et al.*[24] suggested that operation should be considered in patients with a QP/QS of more than 3:1 and acute and refractory clinical deterioration within the first two weeks. Our findings support this view. Our first patient with an inferior infarction had a shunt of 4·8:1 complicated by rapid clinical deterioration within the first 10 hours and needed early surgery. The other three had shunts of 3:1 or less and it was possible to delay operation. Acquired septal defects after inferior infarction are often larger than those associated with anterior infarction and thus carry a worse prognosis[25]; surgical correction is difficult and rarely successful. Our single patient had successful surgery carried out 10 hours after the occurrence of the defect. To delay operation until approximately six weeks after infarction in our other three patients, a combination of drugs which have a positive inotropic effect and those which reduce afterload were used. The latter, that is isosorbide dinitrate, nitroprusside, and labetalol, lower peripheral vascular resistance and impedance to left ventricular ejection, thereby improving systemic blood flow.[26 27] Synhorst *et al.*[28] created ventricular septal defects in dogs. After the administration of vasodilators the size of the shunt was reduced because of the different effects on the total pulmonary and systemic vascular resistances. In patients with post-infarction septal rupture, however, DiSegni *et al.*[27] found that though these agents reduced pulmonary wedge pressure and improved left ventricular function the size of the left-to-right shunt was not altered significantly. If left ventricular function improves and pulmonary artery wedge pressure falls, pulmonary artery pressure will also be reduced. This will offset the reduction in systemic vascular resistance. Thus, in case 4 (Table 3) the systemic flow increased slightly, but pulmonary flow remained unchanged, and hence the flow across the septal defect was unaltered, though QP/QS fell slightly. These agents should be used with caution. In patients with right ventricular involvement a fall in venous return, even in the presence of significant left-to-right shunting, may decrease right ventricular stroke volume.[4] Furthermore, lower blood pressure may reduce renal blood flow, as occurred in two of our patients, who then needed positive inotropic drugs.

Initial attempts at surgical repair were carried out via the right ventricle but were associated with poor results. There was difficulty in defining the borders of the defect, and when multiple defects were present they were concealed by the trabeculae of the right ventricle. The incidence of a residual defect and subsequent mortality was very high. The approach is now from the left ventricle where a clear view of the interventricular septum is obtained.[6 29] The patch is put on from the high pressure side of the defect, diminishing the risk of recurrence. The left ventricle is entered by incising or resecting the area of infarction or the commonly coexisting aneurysm, which three of our patients had. The defect was successfully repaired in three of our patients and no recurrence has been detected. The remaining patient died at operation as a result of extensive infarction and severe coronary atheroma.

References

1 Latham PM. Lecture XXVI. Case of rupture of the heart. In: Lectures on subjects connected with clinical medicine, comprising Diseases of the Heart. London: Longman, 1846; II: 168–76.

2 Lee WY, Cardon L, Slodki SJ. Perforation of infarcted interventricular septum. *Arch Intern Med* 1962; **109:** 731–41.

3 Sanders RJ, Kern WH, Blount SG Jr. Perforation of the interventricular septum complicating myocardial infarction. *Am Heart J* 1956; **51:** 736–48.

4 Fox AC, Glassman E, Isom OW. Surgically remediable complications of myocardial infarction. *Progr Cardiovasc Dis* 1979; **21:** 461–84.

5 Cooley DA, Belmonte BA, Zeis LB, Schnur S. Surgical repair of ruptured interventricular septum following acute myocardial infarction. *Surgery* 1957; **41:** 930–7.

6 Kitamura S, Mendez A, Kay JH. Ventricular septal defect following myocardial infarction. *J Thorac Cardiovasc Surg* 1971; **61:** 186–99.

7 Shumacker HB Jr. Suggestions concerning operative management of postinfarction septal defects. *J Thorac Cardiovasc Surg* 1972; **64:** 452–9.

8 Lufschanowski R, Angelini P, Del Rio C, Hallman GL, Cooley DA, Leachman RD. Ventricular septal rupture, secondary to myocardial infarction. *Chest* 1974; **65:** 59–63.

9 Donahoo JS, Brawley RK, Taylor D, Gott VL. Factors influencing survival following postinfarction ventricular septal defects. *Ann Thorac Surg* 1975; **19:** 648–53.

10 Gowda KS, Loh CW, Roberts R. The simultaneous occurrence of a ventricular septal defect and mitral

insufficiency after myocardial infarction. *Am Heart J* 1976; **92:** 234–36.

11 Kaplan MA, Harris CN, Kay JH, Parker DP, Magidson O. Postinfarctional ventricular septal rupture. *Chest* 1976; **69:** 734–38.

12 James TN. De Subitancis mortibus—XXIV. Ruptured interventricular septum and heart block. *Circulation* 1977; **55:** 934–46.

13 Vlodaver Z, Edwards JE. Rupture of ventricular septum or papillary muscle complicating myocardial infarction. *Circulation* 1977; **55:** 815–22.

14 Selzer A, Gerbode F, Kerth WJ. Clinical, haemodynamic, and surgical considerations of rupture of the ventricular septum after myocardial infarction. *Am Heart J* 1969; **78:** 598–607.

15 Schlesinger Z, Lieberman Y, Landesberg A, Neufeld HN. Repair of ventricular septal defect and left ventricular aneurysm following myocardial infarction. *Thorax* 1971; **26:** 615–8.

16 Hill JD, Lary D, Kerth WJ. Gerbode F. Acquired ventricular septal defects. Evolution of an operation, surgical technique, and results. *J Thorac Cardiovasc Surg* 1975; **70:** 440–50.

17 Iben AB, Pupello DF, Stinson EB, Shumway NE. Surgical treatment of postinfarction ventricular septal defects. *Ann Thorac Surg* 1969; **8:** 252–62.

18 Buckley MJ, Mundth ED, Daggett WM, DeSanctis RW, Sanders CA, Austen WG. Surgical therapy for early complications of myocardial infarction. *Surgery* 1971; **70:** 814–20.

19 Giuliani ER, Danielson GK, Pluth JR, Odyniec NA, Wallace RB. Postinfarction ventricular septal rupture. Surgical considerations and results. *Circulation* 1974; **49:** 455–9.

20 Daggett WM, Guyton RA, Mundth ED, *et al.* Surgery for post-myocardial infarct ventricular septal defect. *Ann Surg* 1977; **186:** 260–71.

21 Stinson EB, Becker J, Shumway NE. Successful repair of postinfarction ventricular septal defect and biventricular aneurysm. *J Thorac Cardiovasc Surg* 1969; **58:** 20–4.

22 Graham AF, Stinson EB, Daily PO, Harrison DC. Ventricular septal defects after myocardial infarction. Early operative treatment. *JAMA* 1973; **225:** 708–11.

23 Windsor HM, Shanahan MX, Chang VP. Perforation of the interventricular septum complicating myocardial infarction. *Med J Aust* 1978; **1:** 587–90.

24 Mundth ED, Buckley MJ, Daggett WM, Sanders CA, Austen WG. Surgery for complications of acute myocardial infarction. *Circulation* 1972; **45:** 1279–91.

25 Kahn J-C, Rigaud M, Gandjbakhch I, Bardet J, Bensaid J, Bourdarias J-P. Posterior rupture of the interventricular septum after acute myocardial infarction: successful early surgical repair. *Ann Thorac Surg* 1977; **23:** 483–6.

26 Tecklenberg PL, Fitzgerald J, Allaire BI, Alderman EL, Harrison DC. Afterload reduction in the management of postinfarction ventricular septal defect. *Am J Cardiol* 1976; **38:** 956–8.

27 DiSegni E, Kaplinsky E, Klein HO, Levy M. Treatment of ruptured interventricular septum with afterload reduction. *Arch Intern Med* 1978; **138:** 1427–9.

28 Synhorst DP, Lauer RM, Doty DB, Brody MJ. Hemodynamic effects of vasodilator agents in dogs with experimental ventricular septal defects. *Circulation* 1976; **54:** 472–7.

29 Javid H, Hunter JA, Najafi H, Dye WS, Julian OC. Left ventricular approach for the repair of ventricular septal perforation and infarctectomy. *J Thorac Cardiovasc Surg* 1972; **63:** 14–24.

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Use of high kilovoltage filtered beam radiographs for detection of bronchial situs in infants and young children

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SUMMARY Determination of atrial situs is of cardinal importance in the analysis of complex congenital heart lesions, and is best predicted from bronchial situs. Previous methods for assessing bronchial morphology, however, are unsuited to the very young patient.

To assess bronchial morphology, 100 consecutive patients under 18 months of age (median 57·5 days) with suspected congenital heart disease were studied by high kilovoltage filtered beam radiographs, before cardiac catheterisation. This low radiation dose technique clearly defined bronchial anatomy in 95 patients. The lengths of the left and right main bronchi were compared and 10 cases (10%) had a ratio less than 1·5 suggesting bronchial isomerism. Discriminant function analysis based on tracheal width and bronchial length enabled clear distinction of right from left bronchi. Four patients had bilateral right and six had bilateral left bronchi. Four of these 10 cases died and had necropsy confirmation of the radiological diagnosis.

Practical prediction about cardiac anatomy, particularly the systemic and pulmonary venous return, may be made when bronchial morphology is known.

The reliable identification of atrial situs is of fundamental importance in the classification of congenital heart disease. The classical method of predicting atrial situs has been to ascertain the position of the abdominal viscera. This method is unreliable when applied to cases with visceral heterotaxy.[1–3] Numerous series have shown a significant association between abnormalities of splenic development (asplenia and polysplenia syndromes) and visceral heterotaxy.[4–11] The use of criteria which suggest asplenia, however, such as the presence of Howell-Jolly bodies in the blood, does not greatly improve correct prediction of atrial situs,[12] and is inapplicable in the newborn. Van Mierop *et al.*[13] first reported the use of penetrated chest radiography to assess bronchial situs and hence atrial situs. Subsequent necropsy evidence has shown that bronchial situs is the most reliable indirect method of predicting atrial situs.[8 9 12 14] Bronchial situs can be reliably and objectively established in life with the use of bronchial tomography.[15] That technique, however, is not easily applied to very young patients, whereas it is in this group that the highest incidence of abnormal atrial situs would be expected.

The present study was designed to see whether bronchial morphology could be determined simply and reliably by high kilovoltage filtered beam radiography in this age group; whether, in practice, the separate entities of bilateral right bronchi (right isomerism) and bilateral left bronchi (left isomerism) could be distinguished in cases of situs ambiguus, and what value the investigation had as a screening technique.

Subjects and methods

High kilovoltage filtered beam radiographs were performed in 100 consecutive patients, under 18 months of age, who presented to The Hospital for Sick Children, Great Ormond Street, with congenital heart disease, over a six-month period. Ninety-one of these patients were under 1 year old and the median age was 57·5 days. Both emergency

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and routine admissions were included in the study, and all patients underwent cardiac catheterisation.

x-RAY TECHNIQUE

The patient was placed face upward on a horizontal Bucky table. The field of interest was a projection of the thorax from above the clavicles to the lower sternum and this field was defined by using the light beam collimator. The *x*-ray beam first passes through a 2 mm layer of aluminium incorporated into the tube housing and collimator box; it then passes through a filter consisting of 0·5 mm of copper and 0·4 mm of tin inserted into the collimator box with the copper layer on the side of the *x*-ray tube.[16–18] A very light grid* was retained to absorb radiation scattered forward. Kilovoltage settings in the range 125 to 140 were used on a three-phase generator. The milli-ampere-seconds were fixed and the kilovoltage setting varied according to patient size. Kodak Ortho G film was used in combination with 3M Alpha 8 speed intensifying screens.

On the exposed radiograph, bone detail is effaced to a considerable degree allowing soft tissue and gas interfaces in the mediastinum and adjacent lung to be seen. Thus the trachea, bronchi, aortic arch, and pulmonary artery conus may be identified. In addition, the lower margin of a normally located left atrium may be visible and the ordinarily dense thymic shadow is seen as a structure of lesser density than the main blood-containing vascular pathways. The calibre of the proximal pulmonary blood vessels near the lung hilum could often be estimated subjectively. The principal concern of this study, however, was the ability to demonstrate the tracheal and proximal bronchial anatomy. The latter was assessed independently by two of the authors (FJM, ARC), and the length of the left and right main bronchi was measured using the technique described by Partridge *et al.*[15] and shown in Fig. 1. To standardise the varying bronchial lengths for each child, the tracheal width at the level of the clavicles was measured. This variable was chosen on empirical grounds because, at this level, the trachea is just outside the thorax, not subject to changes in intrathoracic pressure, and is presumably related to the size of the child. Further, it is magnified to the same degree as the bronchi, so that calculation of the magnification factor is unnecessary.

In all cases, the position of the heart in the chest and the side of the aortic arch in relation to the trachea were recorded from the filter beam radiograph. The frontal P wave axis was measured from the electrocardiogram. In the patients who had isomeric bronchi shown by the filter beam radiographs, the bronchial morphology was checked by observation of the relation of the pulmonary arteries to the tracheobronchial tree in a lateral angiocardiogram, as advocated by Soto and colleagues.[19]

Cardiac catheterisation and angiocardiography were performed to show the precise cardiac anomaly: the presence of bilateral superior vena cavae was sought by contrast injection into the innominate vein, and the course of the inferior vena cava noted. Interruption of the inferior vena cava was diagnosed where the catheter could not be passed directly from the abdominal inferior vena cava to an atrium, but entered the heart via an azygos system on one side or the other. Pulmonary venous drainage was identified by direct catheterisation or on the pulmonary venous phase of a right ventricular or pulmonary artery angiocardiogram. Where the patient underwent cardiac surgery or necropsy, confirmation of the radiological prediction of atrial and bronchial morphology was sought. Necropsies were performed in nine cases.

Statistical analyses of the findings were carried out using the *Statistical package for the social sciences*,[20] together with a brief Fortran IV program to organise data entry.

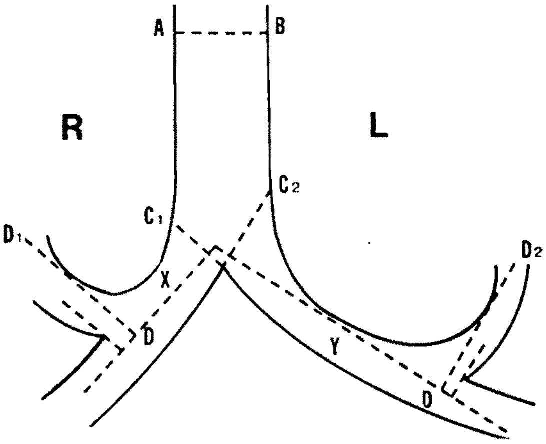

Fig. 1 *Measurement of bronchial length. The mean axes of the main bronchi are first drawn and perpendicular lines to these axes are drawn from the carina. Further perpendicular lines are drawn either tangential to the proximal upper lobe bronchial wall or at the angle of the distal wall with the main bronchus. One of these two lines could always be drawn. The bronchial lengths are then distances between* C_1 *and* D_1 *(X) and* C_2 *and* D_2 *(Y). The tracheal width (AB) was measured at the level of the clavicles (see text).*

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* Ultrafine line moving grid; 40 slats/cm; ratio 8:1.

Results

The high kilovoltage filtered beam radiographs enabled clear definition of bronchial anatomy in 95 patients (Fig. 2 to 4). In five cases the radiographs were not of diagnostic quality as both main bronchi could not be seen to their first division: these cases occurred early in the series when we were less familiar with the technique.

The lengths of the main bronchi to the left and right lungs were compared and the ratios of the bronchial lengths are shown in Fig. 5. Eighty-five patients had a ratio above 1·5, implying situs solitus.[12] Ten patients were clearly different, having a ratio below 1·5, which is diagnostic of bronchial isomerism.[12] Simple examination of the radiographs without any measurements by two of the authors, working independently, proved reliable in differentiating patients with bronchial isomerism from those with situs solitus. It was not possible, however, to distinguish left from right isomerism with certainty without measuring bronchial lengths. In order to make this distinction, the lengths of the left and right main bronchi in the patients with situs solitus (that is those with bronchial ratios above 1·5) were plotted against tracheal width (Fig. 6). Using discriminant function analysis, a linear discriminant equation was calculated based on bronchial length and tracheal width, entry of both of which into the equation was highly significant ($p < 0 \cdot 0005$). Where b = bronchial length (mm) and t = tracheal width (mm) the discriminant function was

$$0 \cdot 292b - 0 \cdot 492t - 2 \cdot 85.$$

When this function is positive the bronchus is classified as left and when negative as right: the morphology of any bronchus can easily be identified by referring to Fig. 6. The 10 patients with bronchial isomerism could be divided into two groups: six patients with bilateral left bronchi (left isomerism) and four with bilateral right bronchi (right isomerism). The clinical data of these patients are shown in the Table.

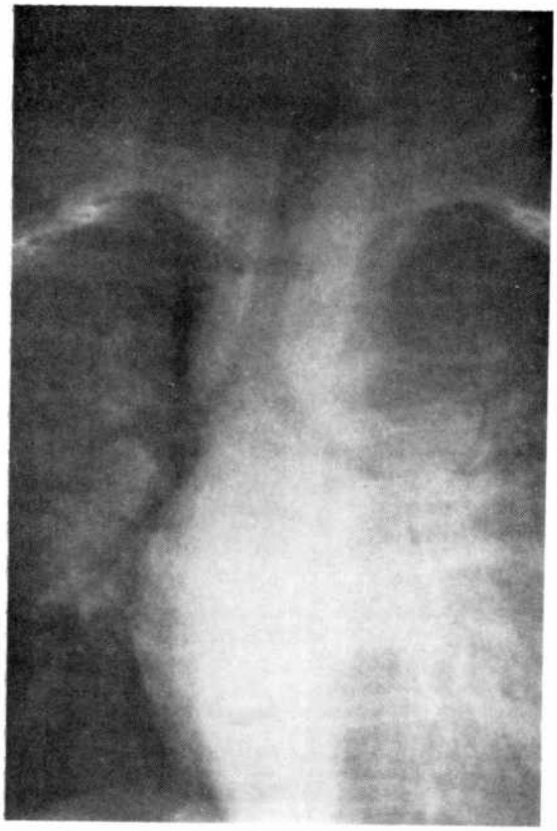

Fig. 2 *Filter beam radiograph showing situs solitus. There is a short bronchus on the right which bifurcates early and a longer curved bronchus on the left.*

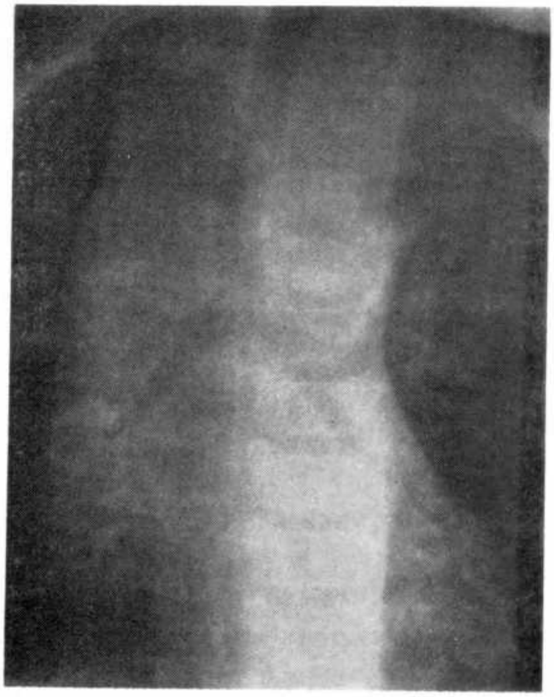

Fig. 3 *Filter beam radiograph showing right isomerism with two short early branching bronchi.*

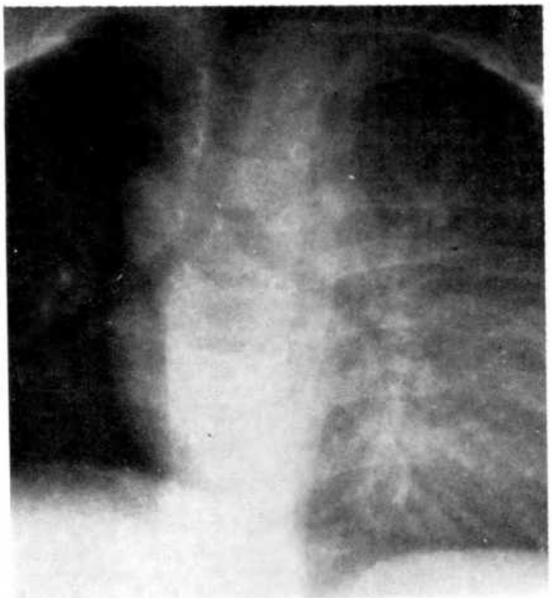

Fig. 4 *Left isomerism with two long curved bronchi. An azygos continuation of the inferior vena cava is clearly seen on the patient's right side.*

LEFT ISOMERISM (six patients)
One patient with a ventricular septal defect died and at necropsy the presence of bilateral left atria and hyparterial bronchi was confirmed. Of the remaining five patients, three had isolated ventricular septal defects, one tetralogy of Fallot, and one a univentricular heart of left ventricular type with pulmonary stenosis. Interruption of the inferior vena cava was found in two patients (33%), and a superiorly orientated p wave axis on the electrocardiogram in one patient (17%). The pulmonary venous drainage was normal in all six cases. No attempt was made to confirm or exclude the presence of polysplenia.

RIGHT ISOMERISM (four patients)
Three of the four patients had univentricular hearts, with pulmonary atresia in two (50%) and pulmonary stenosis in a third. The pulmonary venous drainage was anomalous in these three patients (75%); it was infradiaphragmatic in two and supradiaphragmatic in the third. All three patients died. At necropsy right isomerism of the atria and bronchi was confirmed, and no spleen was found.

No case of bronchial situs inversus was found in the series.

Discussion

The technique of high kilovoltage filter beam radiography enables reliable, high quality visualisation of bronchial anatomy in a very young patient, where breathing blur limits the usefulness of bronchial tomography.[15] This is accomplished with a low radiation dose (probably about one-sixth that of a routine chest radiograph when calcium tungstate intensifying screens are used) and can easily be performed as part of the initial examination. The lengths of the left and right main bronchi

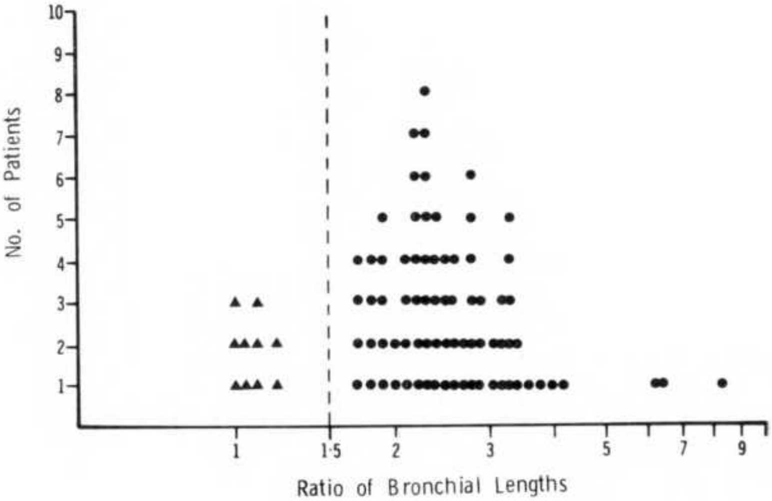

Fig. 5 *Distribution of bronchial length ratios (left to right bronchial ratio).*

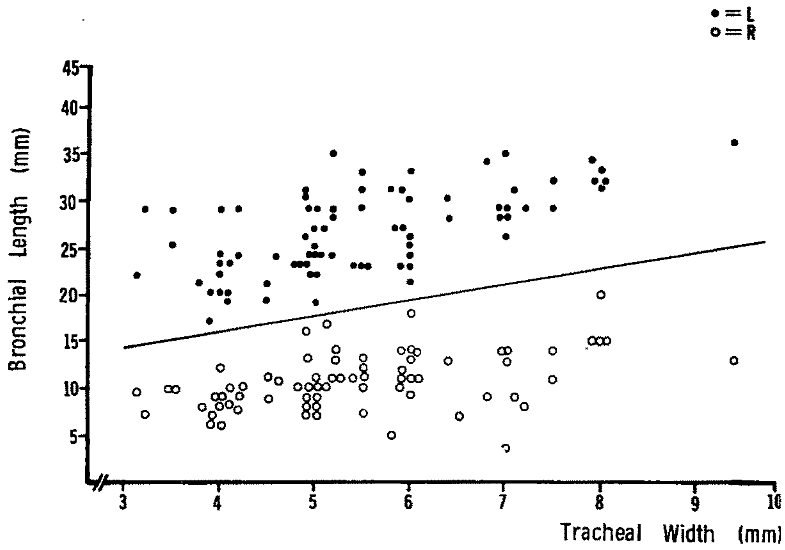

Fig. 6 *Graph of bronchial length of the patients with situs solitus plotted against tracheal width at the level of the clavicles. The solid line represents the discriminant equation dividing left and right bronchi (see text)*

are measured and bronchial isomerism is diagnosed when the ratio of bronchial length is less than 1·5: this can be done without any knowledge of the magnification factors of the equipment. If the ratio is above 1·5, the longer bronchus is morphologically left, and the short bronchus morphologically right. To classify unknown isomeric bronchi into left or right morphology one need only measure tracheal width and refer to Fig. 6. No complex calculations are required.

Bronchial morphology is important because of its relation to atrial morphology. The method of sequential chamber localisation introduced by Van Praagh[21] [22] to classify congenital heart disease is based on the identification of atrial situs. While ventricular morphology and great vessel anatomy are easily diagnosed by angiocardiography, direct identification of atrial morphology is more difficult and requires selective atrial appendage injections of contrast medium. This method has yet to be validated in a large series of patients and is impracticable precisely when it is most needed. Patients with atrial isomerism frequently have exceedingly complex cardiac anatomies, and three selective injections into ventricles or great arteries are often required to demonstrate the ventricular and great artery anatomy. Thus, if contrast medium toxicity is to be avoided, an indirect but reliable method of identifying atrial situs is necessary. Bronchial isomerism was noted in patients with visceral

Table *Data of cases with bronchial isomerism*

Case no.	*Age (w)*	*Sex*	*Position of cardiac apex*	*Aortic arch*	*IVC*	*P wave axis*	*Bronchial lengths (mm)*		*Ratio of lengths*	*Thoracic situs*	*Diagnosis*
							L	*R*			
1	8	F	L	L	R	+ 90	28	27	1·04	L	VSD, polydactyly
2	48	F	L	L	Int	+ 60	30	25	1·2	L	UVH, PS, PDA
3	4	M	L	L	Int	− 60	28	28	1·0	L	VSD
4	44	M	L	L	R	+ 60	22	26	1·23	L	VSD
5	4	F	L	R	R	+ 45	17	18	1·06	L	Tetralogy of Fallot
6	2	M	L	L	R	+105	20	22	1·1	L	VSD*
7	5	F	L	R	R	+ 30	11	12	1·09	R	Tetralogy of Fallot
8	0·3	M	R	R	L	+ 60	11	11	1·0	R	UVH, P atresia,* TAPVD
9	0·14	F	L	L	R	+ 60	13	12	1·1	R	UVH, PS, TAPVD*
10	1	F	L	R	R	+ 90	8	8	1·0	R	UVH, P atresia,* TAPVD

Abbreviations: IVC, inferior vena cava; L, left; R, right; Int, interrupted; VSD, ventricular septal defect; PS, pulmonary stenosis; PDA, persistent ductus arteriosus; UVH, univentricular heart; TAPVD, total anomalous pulmonary venous drainage.
* Diagnosis confirmed at necropsy.

heterotaxy in 1926 by Pernkopf[23] and the close relation between bronchial and atrial situs was observed by later investigators.[7 14 24 25] There are some reports where bronchial situs predicted atrial situs incorrectly[26 27] but in a review of 45 necropsy cases with atrial isomerism, Macartney and colleagues[28] found that atrial situs and thoracic (or bronchial) situs corresponded in all cases. We consider that it is more appropriate to use atrial situs than splenic status to categorise congenital heart lesions. Right atrial isomerism is not always associated with asplenia nor left atrial isomerism with polysplenia.[28] Establishing splenic status in life is difficult, whereas establishing thoracic situs is easy using filter beam radiographs. Such radiographs avoid the technical problems inherent in bronchial tomography in infants. This present study was limited to infants and toddlers, but our experience of the technique applied to older children with suspected anomalies of situs suggests that image quality is as good as that obtained with standard tomography.

We found a high incidence (10%) of bronchial isomerism among our 100 cases of congenital heart disease below the age of 18 months, and subsequent experience with the technique has confirmed this finding. Indeed it is in these very young patients that the highest incidence of situs ambiguus would be expected, for the associated cardiac lesions often carry a poor prognosis. We have no means of comparing our results with those of other centres as there are no previously reported series of *in vivo* determination of atrial situs in this age group.

The early identification of atrial situs has a distinct practical advantage and is not only of value in the correct description of complex congenital heart defects. Using filter beam radiographs one can distinguish left isomerism from right isomerism, and this enables several important predictions to be made about the cardiac anatomy. Left isomerism is associated among other lesions with interruption of the inferior vena cava (as found in one-third of our patients), so one should think carefully before deciding to catheterise such patients from the leg. Patients with right isomerism have a high incidence of univentricular heart, ventricular septal defect, and pulmonary stenosis or atresia. In right isomerism, total anomalous pulmonary venous return is frequent (75% of our patients), and it is important to be prepared for this possibility before cardiac catheterisation. If, because of low pulmonary blood flow, the amount of oxygenated blood returning to the systemic circulation is small, anomalous pulmonary venous return can easily be missed both on oximetry and angiocardiography. Should this mishap occur then the patient may undergo a systemic-pulmonary shunt for low pulmonary blood flow and die from pulmonary oedema because of unrelieved obstructed total anomalous pulmonary venous drainage.

In addition to showing tracheal and bronchial anatomy, the filtered beam radiograph provides an opportunity of defining mediastinal structures which on the orthodox chest radiograph may be obscured by thymus, sternum, and spine. The absence of a main pulmonary artery conus may be noted in pulmonary atresia. In the central parts of the lung adjacent to the hilum, the position and calibre of vascular structures may be assessed. The size of the normally located left atrium may be inferred not only from the angle which the main bronchi form with each other, but also from the convexity of the lower margin of the left atrium. If the main bronchi are of narrow calibre, compression by vascular structures such as large pulmonary arteries may be suspected as a cause for tachypnoea, or even stridor and air trapping. One learns swiftly to identify on which side of the trachea the aortic arch lies from the radiograph.

In summary, the filtered beam radiograph supplants much of the need for tomography for the determination of bronchial situs, not only in patients with heart disease but also in patients with non-cardiac problems. By establishing bronchial situs, atrial situs can be predicted quickly and safely in the very young patient.

References

1 Liberthson RR, Hastreiter AR, Sinha SN, Bharati S, Novak GM, Lev M. Levocardia with visceral heterotaxy-isolated levocardia: pathologic anatomy and its clinical implications. *Am Heart J* 1973; **85:** 40–54.

2 Lev M, Liberthson RR, Eckner FAO, Arcilla RA. Pathologic anatomy of dextrocardia and its clinical implications. *Circulation* 1968; **37:** 979–99.

3 Lev M, Liberthson RR, Golden JG, Eckner FAO, Arcilla RA. The pathologic anatomy of mesocardia. *Am J Cardiol* 1971; **28:** 428–35.

4 Ivemark BI. Implications of agenesis of the spleen on the pathogenesis of cono-truncus anomalies in childhood. *Acta Paediatr Scand* 1955; **44,** suppl: 104.

5 Putschar WGJ, Manion WC. Congenital absence of the spleen and associated anomalies. *Am J Clin Pathol* 1956; **26:** 429–70.

6 Ruttenberg HD, Neufeld HN, Lucas RV Jr, *et al.* Syndrome of congenital cardiac disease with asplenia: distinctive from other forms of congenital cyanotic cardiac disease. *Am J Cardiol* 1964; **13:** 387–406.

7 Moller JH, Nakib A, Anderson RC, Edwards JE. Congenital cardiac disease associated with polysplenia. *Circulation* 1967; **36:** 789–99.

8 Van Mierop LHS, Gessner IH, Schiebler GL. Asplenia and polysplenia syndrome. In: Bergsma D, ed. *Birth defects original article series*. Vol VIII, No. 5. *Congenital cardiac defects—recent advances*. Baltimore. Williams & Wilkins, 1972: 36–44.

9 Van Mierop LHS, Gessner IH, Schiebler GL. Asplenia and polysplenia syndrome. In: Bergsma D, ed. *Birth defects original article series*. Vol III, No. 1. *Congenital cardiac defects—recent advances*. Baltimore: Williams & Wilkins, 1972: 74–82.

10 Freedom RM. The asplenia syndrome: a review of significant extracardiac structural abnormalities in 29 necropsied patients. *J Pediatr* 1972; **81:** 1130–3.

11 Rose V, Izukawa T, Möes CAF. Syndromes of asplenia and polysplenia. A review of cardiac and non-cardiac malformations in 60 cases with special reference to diagnosis and prognosis. *Br Heart J* 1975; **37:** 840–52.

12 Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977*. Edinburgh and London: Churchill Livingstone, 1978: 16–26.

13 Van Mierop LHS, Eisen S, Schiebler GL. The radiographic appearance of the tracheobronchial tree as an indicator of visceral situs. *Am J Cardiol* 1970; **26:** 432–7.

14 Stanger P. Rudolph AM, Edwards JE. Cardiac malpositions. An overview based on study of sixty-five necropsy specimens. *Circulation* 1977; **56:** 159–72.

15 Partridge JB, Scott O, Deverall PB, Macartney FJ. Visualisation and measurement of the main bronchi by tomography as an objective indicator of thoracic situs in congenital heart disease. *Circulation* 1975; **51:** 188–96.

16 Dunbar JS. Upper respiratory tract obstruction in infants and children. *Am J Roentgenol* 1970; **109:** 227–46.

17 Joseph PM, Berdon WE, Baker DH, Slovis TL, Haller JO. Upper airway obstruction in infants and small children. *Radiology* 1976; **121:** 143–8.

18 Wolf EL, Berdon WE, Baker DH. Improved plain film diagnosis of right aortic arch anomalies with high kilovoltage-selective filtration-magnification technique. *Pediatr Radiol* 1978; **7:** 141–6.

19 Soto B, Pacifico AD, Souza AS Jr, Bargeron LM Jr, Ermocilla R, Tonkin IL. Identification of thoracic isomerism from the plain chest radiograph. *Am J Roentgenol* 1978; **131:** 995–1002.

20 Nie NH, Hull CH, Jenkins JG, Steinbrenner K, Bent DH. *Statistical package for the social sciences*. 2nd ed. New York: McGraw Hill, 1975.

21 Van Praagh R. The segmental approach to diagnosis in congenital heart disease. In Bergsma D, ed. *Birth defects original article series. Congenital cardiac defects—recent advances*. Baltimore: Williams & Wilkins, 1972: 4–23.

22 Van Praagh R, Van Praagh S, Vlad P, Keith JD. Anatomic types of congenital dextrocardia. Diagnostic and embryologic implications. *Am J Cardiol* 1964; **13:** 510–31.

23 Pernkopf E. Der partielle Situs inversus der Eingeweide beim Menschen. Gedanken zum Problem der Asymmetrie und zum Phannomen der Inversion. *Z Gesamte Anat* 1926; **79:** 577–752.

24 Van Mierop LHS, Wiglesworth FW. Isomerism of the cardiac atria in the asplenia syndrome. *Lab Invest* 1962; **11:** 1303–15.

25 Landing BH, Lawrence TYK, Payne VC Jr, Wells TR. Bronchial anatomy in syndromes with abnormal visceral situs, abnormal spleen and congenital heart disease. *Am J Cardiol* 1971; **28:** 456–62.

26 Brandt PWT, Calder AL. Cardiac connections: the segmental approach to radiologic diagnosis in congenital heart disease. *Curr Probl Diagn Radiol* 1977; **7:** 1–35.

27 Caruso G, Becker AE. How to determine atrial situs? Considerations initiated by three cases of absent spleen with a discordant anatomy between bronchi and atria. *Br Heart J* 1979; **41:** 559–67.

28 Macartney FJ, Zuberbuhler JR, Anderson RH. Morphologic considerations pertaining to the recognition of atrial isomerism—their consequences for sequential chamber localisation. *Br Heart J* 1980; in press.

Requests for reprints to Professor F J Macartney, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

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Haemodynamic effects of haematocrit reduction in patients with polycythaemia secondary to cyanotic congenital heart disease

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SUMMARY Acute reduction in haematocrit (without significant alteration of blood volume) in six patients with severe polycythaemia secondary to cyanotic congenital heart disease resulted in an increase in resting cardiac output without alteration in heart rate. Cardiac output was also increased during a constant-load exercise test after haematocrit reduction, and under these conditions total oxygen uptake was increased with consequent reduction in oxygen debt. These measurements confirm that the subjective improvement in such patients after haematocrit reduction is matched by physiological circulatory changes.

Patients with cyanotic congenital heart disease and secondary polycythaemia feel subjectively improved after venesection, the clinical manifestations of headache, lethargy, breathlessness, and anorexia being attributed to the increased haematocrit with attendant raised blood viscosity and intravascular red cell aggregation.[1] The circulatory response to reduction in haematocrit has been assessed previously in such patients at rest,[2] there being a reduction in peripheral vascular resistance and an increase in cardiac output, stroke volume, systemic blood flow, and systemic oxygen transport.

We have extended this work to investigate the effects of haematocrit reduction in patients with polycythaemia secondary to congenital heart disease, both at rest and during exercise.

Methods

Six patients with cyanotic congenital heart disease and secondary polycythaemia were studied. The initial haemoglobin level in each patient was greater than 20 g/dl. The underlying cardiac pathology was as follows. Case 1, a man of 39 years with an univentricular heart (and fixed rate pacemaker); case 2, a man of 20 years with a ventricular septal defect and the Eisenmenger syndrome; case 3, a girl of 15 years with transposition of the great arteries with pulmonary stenosis and ventricular septal defect; case 4, a girl of 18 with tetralogy of Fallot; case 5, a 26-year-old man with tetralogy of Fallot; and case 6, a 16-year-old boy with tetralogy of Fallot.

Each patient had haemoglobin, packed cell volume, and blood viscosity measurements made and was then subjected to an increasing work load on a bicycle ergometer (Siemens electrically stabilised load cycle ergometer). The equipment used during this test is shown in Fig. 1. The subject breathed through a mouth-piece with a unidirectional flow valve, and inspired ventilation was measured using a dry gas meter (Parkinson-Cowan) connected to a Mingograph recorder. The expired air passed through a valve box into a mixing chamber; air was sampled from this chamber continuously and passed over silica gel to remove water vapour. The dried mixed expired air passed to a mass spectrometer for oxygen and carbon dioxide measurement.

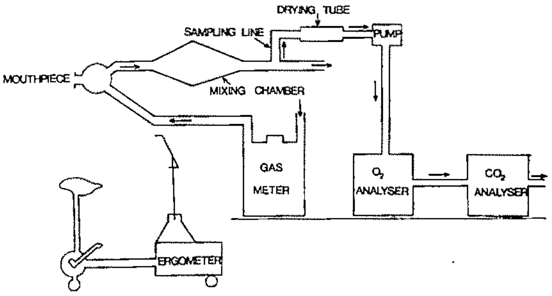

Fig. 1 *Circuit diagram of the exercise equipment.*

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The initial work load was 100 kpm/min. If the patient was able to maintain exercise at this load for six minutes, he was allowed to rest and the test repeated at successive load increments of 100 kpm/min. In this way maximal work capacity could be assessed. This procedure was repeated three times to ensure that the maximal work capacity measured was not influenced in any way by a process of learning. As a safety precaution, exercise was stopped if the heart rate reached 85 per cent of the maximum predicted for age.

The patients were then exposed to a constant work load of six minutes duration, the power output selected being 50 per cent of the maximum work load previously ascertained. A steady resting state before starting this test was taken as the point where the ventilatory rate and mixed expired gas concentrations were constant. At this stage, a blood sample was taken for blood gas analysis from a vasodilated ear lobe. Blood gases were measured on this sample using a Corning 165 blood gas analyser. Ear lobe blood is virtually identical to arterialised blood.[3] Baseline measurements of heart rate, ventilatory rate, $\mathrm{Feo_2}$ and $\mathrm{Feco_2}$ (fractional concentrations of oxygen and carbon dioxide in expired air in mmHg respectively), were also made. Using these measurements O_2 uptake/min at rest could be calculated using the equation:

$$\dot{V}\mathrm{o_2} = \dot{V}_\mathrm{i} \times 0{\cdot}2093 - \frac{0{\cdot}7903}{1{\cdot}00-(\mathrm{Feco_2}+\mathrm{Feo_2})} \times \mathrm{Feo_2} \times \mathrm{STPD}$$

where $\dot{V}\mathrm{o_2}$ = volume uptake of oxygen per unit time (l/min)
$\dot{V}_\mathrm{i}$ = inspired ventilation of air (l/min)
STPD = standard temperature and pressure

$$\mathrm{dry} = \frac{273}{(273+T)} \times \frac{(\mathrm{Pbar-SVP})}{760}$$

Before the start of the constant work load test, resting cardiac output was also measured using the Fick principle. The Fick equation is given below:

$$\text{Cardiac output} = \frac{\dot{V}\mathrm{co_2}}{\mathrm{C_vco_2 - C_aco_2}}$$

where $\dot{V}\mathrm{co_2}$ = volume production of $\mathrm{Co_2}$ per unit time (l/min) and is given by

$$\dot{V}\mathrm{co_2} = \frac{\mathrm{Feco_2} \times \dot{V}_\mathrm{i} \times 0{\cdot}7903}{1{\cdot}00-(\mathrm{Feco_2}+\mathrm{Feo_2})} \times \mathrm{STPD}$$

$\mathrm{C_vco_2}$ = content (volume per 100 ml) of carbon dioxide in venous blood.
$\mathrm{C_aco_2}$ = content (volume per 100 ml) of carbon dioxide in arterial blood.

All these values with the exception of $\mathrm{C_vco_2}$ were known and therefore to measure cardiac output $\mathrm{C_vco_2}$ had to be measured. This was done using a rebreathing technique with a 7 per cent carbon dioxide, 93 per cent oxygen mixture, the patient being connected to a bag containing this gas mixture via a pneumatic valve and then encouraged to breathe quickly and deeply in and out for four breaths to mix the gas in the bag with that in the lungs. After four breaths the patient was encouraged to breathe steadily for the remainder of a 20 second period, which produced an equilibrium pattern as shown in Fig. 2. An acceptable equilibrium should be produced between five and 10 seconds after the onset of the breathing procedure. During the plateau phase, lung, bag, and mixed venous blood are in equilibrium. The value for $\mathrm{P_vco_2}$ obtained in this way is slightly higher than true mixed venous $\mathrm{Pco_2}$ in pulmonary capillary blood. The reasons for this are not fully understood, but an appropriate correction can be made using the following formula: $\mathrm{P_vco_2}$ (corrected) = equilibrium $\mathrm{Pco_2}$ $-(0{\cdot}23\times$ equilibrium $\mathrm{Pco_2})-10$.

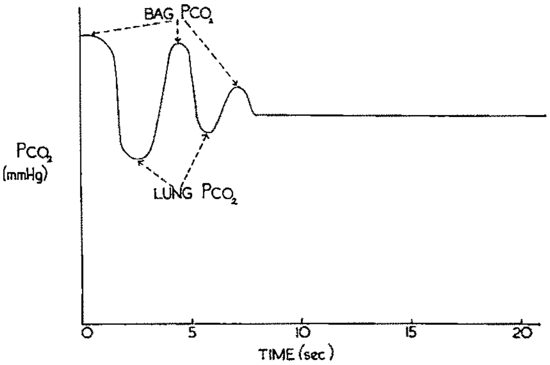

Fig. 2 *Typical result from rebreathing experiment to measure content of CO_2 in venous blood.*

Using this value, resting cardiac output could be measured.

The true constant work load exercise test was then started. The patient was exercised at 50 per cent maximal working capacity for six minutes with continuous assessment of heart rate, inspired ventilatory rate, $\mathrm{Feo_2}$, and $\mathrm{Feco_2}$. Values for heart rate, ventilation rate, and oxygen uptake during the sixth minute of exercise were then compared with the values for these at rest to assess the patient's response to exercise. A sample of ear lobe blood was also taken during the sixth minute for estimation of blood gases. Towards the end of the sixth minute, the patient was connected again to a bag containing 7 per cent carbon dioxide, 93 per cent oxygen, and $\mathrm{P_vco_2}$ estimated as before, thus allowing cardiac output during exercise to be measured.

By calculating oxygen uptake at each minute for six minutes, a plot of oxygen uptake against time could be produced (Fig. 3) during the constant work load. In all cases, equilibrium for oxygen uptake was established by the fourth minute. Thereafter, the value for oxygen uptake remained constant. The shaded area on this plot (Fig. 3) can therefore be taken as an estimate of oxygen debt, and was measured using planimetry.

Each patient was then venesected, three pints of blood being withdrawn, with three pints of plasma given as intravenous replacement. Three and 14 days later, the above procedures were repeated.

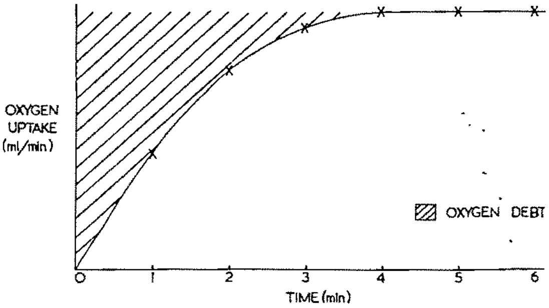

Fig. 3 *Typical plot of O_2 uptake against time during constant work load exercise test; hatched area represents the oxygen debt.*

Results

All results given are mean ± standard error of the mean. Differences between groups have been compared using Students' t test.

Mean values for haemoglobin and packed cell volume fell significantly from 22·4 ± 0·5 g/dl and 66 ± 1 per cent before venesection to 18·6 ± 0·4 g/dl (p < 0·01) and 58 ± 1 per cent (p < 0·01) three days after venesection. This reduction was maintained on the 14th day after venesection: haemoglobin 18·8 ± 0·5 g/dl (p < 0·01), packed cell volume 58 ± 1 per cent (p < 0·01). Table 1 shows the results for each individual. There was a corresponding fall in viscosity from 6·61 ± 0·12 before venesection to 5·29 ± 0·13 three days after venesection and 5·32 ± 0·13 14 days after venesection. In association with these changes in haemoglobin, packed cell volume, and viscosity, there was an increase in maximal exercise capacity from 333 ± 30 kpm/min before venesection to 500 ± 48 kpm/min three days afterwards (p < 0·01) and 483 ± 43 kpm/min 14 days afterwards (p < 0·01). There was also a significant increase in resting cardiac index from 2·2 ± 0·1 before to 2·9 ± 0·2 (p < 0·01) at both three and 14 days after venesection, without significant change in heart rate. This implies an increase in mean stroke volume in these patients. There was no significant change in resting PAo_2 and $PAco_2$ after venesection. The mean values for oxygen uptake rose (325, 358, and 375 ml/min) and the mean values for ventilatory rate fell (12·9, 12·7, and 12·1 l/min), both sets of figures respectively before venesection and three and 14 days after venesection, but these were not significant changes. During the sixth minute of a steady-state exercise test, there was a significant increase in cardiac index at both three and 14 days after venesection as compared with measurements before venesection (Table 2). If the results are related to the values before venesection with this as unity, then the mean cardiac index was 1·14 at three days, and 1·18 at 14 days after venesection. There was a similar increase in normalised

Table 1 *Patients at rest*

Case No.		*Hb (g/dl)*	*PCV (%)*	*Viscosity (centipoise)*	*Heart rate (beats/min)*	*Cardiac index (l/min per m²)*	*PAo_2 (mmHg)*	*$PAco_2$ (mmHg)*	*O_2 uptake (ml/min)*	*Ventilation (l/min)*	*Maximal exercise capacity (kpm/min)*
1	Before venesection	21·3	65	6·42	76	2·0	58	39	304	11·9	200
	3 days after	18·2	58	5·16	76	2·4	61	37	385	11·2	400
	14 days after	18·4	58	5·20	74	2·4	56	36	389	10·9	400
2	Before venesection	21·0	62	6·40	78	2·1	63	36	297	13·8	400
	3 days after	18·4	55	4·96	80	2·6	59	37	286	14·6	500
	14 days after	18·5	55	4·98	82	2·5	60	37	277	13·6	500
3	Before venesection	22·6	67	6·68	60	2·3	61	37	398	12·6	300
	3 days after	18·1	57	5·04	64	3·4	64	38	416	12·9	500
	14 days after	18·2	57	5·13	64	3·5	66	36	480	11·6	500
4	Before venesection	24·6	70	6·96	64	2·4	53	37	340	14·6	300
	3 days after	19·5	61	6·01	60	2·9	58	39	360	14·2	400
	14 days after	19·9	61	5·96	60	3·0	58	37	395	14·8	400
5	Before venesection	21·6	64	—	74	2·1	60	36	304	10·9	400
	3 days after	18·3	58	—	70	3·1	64	38	314	10·6	600
	14 days after	18·1	57	—	72	3·4	64	38	330	10·0	600
6	Before venesection	23·4	68	—	82	2·6	56	38	306	13·6	400
	3 days after	19·2	60	—	76	3·0	66	37	386	12·6	600
	14 days after	19·6	60	—	72	2·8	62	40	381	12·0	500

Table 2 *Patients in 6th minute of steady state exercise test (½ max work load before venesection)*

Case No.		*Heart rate (beats/min)*	*Cardiac index (l/min per m^2)*	*PAo_2 (mmHg)*	*$PAco_2$ (mmHg)*	*O_2 uptake (ml/min)*	*Ventilation (l/min)*	*O_2 debt over 6 min (ml)*
1	Before venesection	76	4·1 (1·00)	53	41	1173 (1·00)	26·0	1346 (1·00)
	3 days after	76	4·6 (1·12)	55	38	1264 (1·08)	24·7	1308 (0·97)
	14 days after	76	4·7 (1·15)	55	37	1297 (1·11)	27·3	1304 (0·97)
2	Before venesection	118	5·3 (1·00)	60	37	774 (1·00)	29·3	569 (1·00)
	3 days after	120	6·0 (1·13)	58	39	866 (1·12)	26·7	463 (0·81)
	14 days after	110	6·4 (1·21)	58	37	879 (1·14)	28·8	447 (0·79)
3	Before venesection	114	6·4 (1·00)	55	40	1064 (1·00)	38·3	836 (1·00)
	3 days after	104	7·7 (1·20)	58	36	1273 (1·20)	36·7	574 (0·69)
	14 days after	106	7·7 (1·20)	57	37	1146 (1·08)	40·3	596 (0·71)
4	Before venesection	124	4·7 (1·00)	60	37	1046 (1·00)	35·6	965 (1·00)
	3 days after	120	5·9 (1·26)	64	36	1346 (1·29)	34·4	630 (0·65)
	14 days after	124	5·8 (1·23)	56	37	1262 (1·2)	30·3	646 (0·67)
5	Before venesection	118	7·1 (1·00)	62	32	1270 (1·00)	30·6	646 (1·00)
	3 days after	104	7·7 (1·08)	66	36	1346 (1·06)	30·9	503 (0·78)
	14 days after	124	8·4 (1·18)	64	36	1387 (1·09)	33·0	487 (0·75)
6	Before venesection	118	6·2 (1·00)	58	38	996 (1·00)	26·4	816 (1·00)
	3 days after	106	6·7 (1·08)	62	36	1162 (1·17)	25·6	496 (0·61)
	14 days after	118	6·8 (1·10)	61	41	1188 (1·19)	25·8	537 (0·66)

Values in brackets are normalised for comparison in relation to measurements before venesection.

O_2 uptake from 1·0 to 1·15 and 1·14 at three and 14 days. Normalised O_2 debt, however, fell from 1·0 to 0·75 and 0·76, respectively. There was no difference in the response of heart rate, PAo_2, $PCco_2$ or ventilatory rate to exercise between measurements before and after venesection.

Discussion

The development of secondary polycythaemia with cyanotic congenital heart disease is a compensatory phenomenon in response to the low arterial oxygen tension. The polycythaemia, unlike that of polycythaemia rubra vera, is characterised by increased haematocrit (and therefore red cell volume) with normal circulatory whole blood volume.[4] Theoretically, the increased red cell volume should provide an increased oxygen-carrying capacity[5 6]; this effect, however, is offset by the increase in viscosity which affects blood flow and therefore tissue perfusion.[1] One direct effect of increased viscosity is a reduction in cardiac output[7 8]; a second is increased plasma skimming. (When blood is flowing along a vessel, there is a tendency for cells to concentrate in the core of the lumen creating a "relatively cell-free layer" of plasma close to the vessel wall. Capillaries branching off from such vessels are therefore supplied with blood containing a greater percentage of plasma than red blood cells than elsewhere; this effect is called plasma skimming.) As a result of increased plasma skimming, perfusion of peripheral tissues (and therefore oxygen transfer) will be impaired. Similarly in the lungs, oxygen uptake will be reduced because of increased ventilation—perfusion mismatch. It is obvious therefore that the development of polycythaemia confers some advantages on the individual but also some disadvantages. The physiological effects on the circulation of venesection with fluid replacement have not as yet been fully investigated; we carried out such studies in patients both at rest and during exercise.

At rest, in association with the fall in haematocrit, there was an increase in cardiac index without change in heart rate, implying an increased stroke volume. Similar results were found by Rosenthal *et al.*[2] and were thought to be the result of a fall in peripheral vascular resistance consequent on reduced viscosity. These workers also noted a substantial improvement in systemic oxygen transport, defined as the amount of oxygen supplied but not extracted by the tissues per minute per unit weight of body. They attributed this increase in oxygen transport primarily to increase in systemic blood flow since oxygen-carrying capacity is always reduced and arterial oxygen saturation often declines as a result of haematocrit reduction. They postulated that the advantage of an increase in oxygen transport after isovolaemic red cell volume reduction was in the provision of a greater oxygen reserve available for tissue utilisation on exercise. Murray *et al.*[9] showed that maximum systemic oxygen transport usually occurred at normal haematocrit values. In our study, mean oxygen uptake at rest increased after venesection, but the results failed to reach statistical significance.

During exercise, a significant increase ($p < 0{\cdot}01$) in cardiac index was again noted at both three and 14 days after venesection when compared with values before venesection. In addition, during exercise there was a significant increase ($p < 0{\cdot}05$) in oxygen uptake; consequently O_2 debt was reduced

($p < 0{\cdot}05$). The increase in oxygen uptake could be explained on the basis of improved circulation to peripheral tissues (reduced vascular resistance, reduced plasma skimming) and improved circulation to the capillary bed of the lung (reduced ventilation—perfusion mismatch) as described above. If the transfer of oxygen from the lungs to the blood, and the blood to the tissues is improved, oxygen debt during exercise would theoretically be reduced.

This study, then, confirms that the subjective improvement in patients with cyanotic congential heart disease and secondary polycythaemia is matched by objective changes, there being an increase in both cardiac output and oxygen uptake by peripheral tissues.

References

1 Replogle RL, Meiselman HJ, Merrill EW. Clinical implications of blood rheology studies. *Circulation* 1967; **36:** 148–60.

2 Rosenthal A, Nathan DG, Marty AT, *et al.* Acute hemodynamic effects of red cell volume reduction in polycythemia of cyanotic congenital heart disease. *Circulation* 1970; **42:** 297–307.

3 Godfrey S, Wozniak ER, Courtenay-Evans RJ, Samuels CS. Ear lobe blood samples for blood gas analysis at rest and during exercise. *Br J Dis Chest* 1971; **65:** 58–64.

4 Vérel D. Blood volume changes in cyanotic congenital heart disease and polycythemia rubra vera. *Circulation* 1961; **23:** 749–53.

5 Murray JF, Gold P, Johnson BL Jr. The circulatory effects of haematocrit variations in normovolemic and hypervolemic dogs. *J Clin Invest* 1963; **42:** 1150–9.

6 Richardson TQ, Guyton AC. Effects of polycythemia and anemia on cardiac output and other circulatory factors. *Am J Physiol* 1959; **197:** 1167–70.

7 Dill DB. *Life, heat and altitude.* London and Oxford: Harvard University Press, 1938: 132–5.

8 Pugh LGCE. Cardiac output in muscular exercise at 5,800 m (19,000 ft). *J Appl Physiol* 1964; **19:** 441–7.

9 Murray JF, Gold P, Johnson BL Jr. Systemic oxygen transport in induced normovolemic anemia and polycythemia. *Am J Physiol* 1962; **203:** 720–4.

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Efficacy of intravenous procainamide infusion in converting atrial fibrillation to sinus rhythm

Relation to left atrial size

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SUMMARY The efficacy of intravenous procainamide, infused at 30 mg/min to a maximum dose of 20 mg/kg, in converting atrial fibrillation was evaluated under electrocardiographic and blood pressure control in 21 patients. Nine patients had atherosclerotic heart disease, seven had valvular lesions, five had hypertension, and six had no apparent heart disease. Nine patients (converters), who reverted to sinus rhythm at a mean dose of procainamide of 13·3±3·6 mg/kg (mean plasma concentration, 7·4±3·9 μg/ml) had normal echocardiographic left atrial diameters. All but one of the remainder, the 12 non-converters, who received a mean drug dose of 13·1±3·5 mg/kg (mean plasma concentration 13·9±7·6 μg/ml), had atrial diameters exceeding 4·0 cm. QRS and QTc intervals were not altered significantly in converters, but were prolonged significantly in non-converters. No serious side effects from the infusion were encountered. Intravenous procainamide infusion appears to be a safe and rapidly effective method of converting recent-onset atrial fibrillation to sinus rhythm in patients with normal left atrial dimensions.

Atrial fibrillation associated with acute haemodynamic deterioration is often best controlled by immediate direct current countershock. If the clinical situation does not constitute an emergency, however, the ventricular response may be controlled first by digoxin or propranolol, and elective cardioversion attempted subsequently, either using oral quinidine or electroversion. Neither approach is universally applicable. A method using brief intravenous infusion of an antifibrillatory drug, if effective and safe, is simpler and preferable to electrical defibrillation or to conversion after prolonged oral drug administration. Procainamide, in spite of its pharmacological similarities to quinidine,[1–3] has been used little for this purpose.

Both quinidine and procainamide are membrane-stabilising or class I drugs.[1 3 4] Both also prolong the effective refractory period and raise the threshold of excitability without changing the resting membrane voltage.[3 5] It is, therefore, not unreasonable to expect procainamide to be at least as effective as quinidine in converting atrial fibrillation to normal sinus rhythm, with the added advantage of greater flexibility of parenteral administration because of lower toxicity.

While the effectiveness of procainamide in the control of ventricular arrhythmias is well documented, there is little information about its effect on atrial arrhythmias. Preliminary data from this institution suggested that the rapidity of conversion with procainamide compared favourably with that of direct current countershock without the attendant problems of the latter. We assessed the effects of procainamide infusion on the rapid conversion of atrial fibrillation, with particular reference to left atrial size.

Patients and methods

Twenty-one patients, 12 men and nine women, aged 27 to 84 years (mean, 63 years), with new or paroxysmal atrial fibrillation, were studied (Table 1). The following patients were excluded: (1) those already receiving procainamide; (2) those having known toxicity or hypersensitivity to procainamide; (3) those having advanced (second or third degree) atrioventricular block; or (4) those having received

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digitalis within the preceding six hours. Procainamide in a concentration of 30 mg/ml dissolved in 5 per cent dextrose in water, was infused at a rate of 30 mg/min to one of several end-points: (1) maximum dose, arbitrarily defined as 20 mg/kg; (2) conversion to normal sinus rhythm; (3) hypotension, defined as greater than a 20 per cent fall in systolic blood pressure; (4) QRS or QTc prolongation to greater than 130 per cent of control; or (5) development of second or third degree atrioventricular block.

A baseline 12 lead electrocardiogram, 60-second lead II rhythm strip, and supine blood pressure were recorded just before the start of drug infusion. Cuff blood pressure was determined every three minutes throughout the infusion period and at five-minute intervals until stabilisation thereafter. Continuous monitoring and data storage of lead II throughout the infusion period was done in six patients using a Wolff MR-41CD physiological tape recorder interfaced with a Hewlett-Packard Model no. 78303A 4-channel oscilloscope. In the others, 15-second rhythm strips at 25 mm/s paper speed were obtained during each minute of infusion. The ventricular rate at the end of each minute of infusion was determined by averaging 15 cardiac cycles. No attempt was made to record the atrial fibrillatory rate from the surface tracings because

Table 1 *Clinical features of patients with atrial fibrillation treated with procainamide*

			Atrial fibrillation						
Case no.	*Age (y)*	*Sex*	*Suspected aetiology*	*Duration*	*Blood pressure (initial, mmHg)*	*Ventricular rate (initial, beats/min)*	*NYHA*	*Associated diagnosis*	*Previous history*
(A) Converters (CV)									
1	70	M	Idiopathic	4 h	130/100	130	0		Palpitation
2	40	M	Hypertension	1 d	120/90	158	0		
3	51	M	Idiopathic	1 d	120/80	100	0		Atrial fibrillation
4	84	F	Atherosclerotic heart disease	1 d	90/70	160	I	LBBB, acute pancreatitis, septicaemia	
5	57	F	Idiopathic	6 h	118/68	164	0	Hypothyroidism	Palpitation
6	65	M	Hypertension, atherosclerotic heart disease	7 h	142/100	110	I		Palpitation
7	62	M	Atherosclerotic heart disease	<24 h	103/50	130	II	PUO	Atrial fibrillation
8	51	M	Atherosclerotic heart disease, aortic valve disease (stenosis and regurgitation)	2 h	108/74	100	I	Acute myocardial infarction	
9	27	M	Idiopathic	3 h	108/75	107	0		
(B) Non-converters (NCV)									
10	72	M	Atherosclerotic heart disease, mitral valve prolapse	1 d	150/90	100	0	Myxoedema	Palpitation
11	40	F	Mitral regurgitation, aortic regurgitation	2 d	120/90	158	I	Marfan's disease	
12	78	F	Hypertension, atherosclerotic heart disease	1 d	108/64	110	II	Chronic obstructive pulmonary disease, pulmonary embolus	
13	77	M	Atherosclerotic heart disease	1 d	103/50	98	I		
14	71	F	Idiopathic	30 h	116/72	125	0	Diabetes mellitus, obesity	Palpitation
15	71	F	Hypertension, atherosclerotic heart disease	3 mth	176/120	70	0		
16	79	F	Idiopathic	1 h	148/57	170	I	Lymphoma, congestive heart failure, pneumonia	
17	50	M	Rheumatic heart disease (mitral stenosis and regurgitation)	5 d	126/70	114	I		
18	66	F	Rheumatic heart disease (mitral stenosis)	5 h	160/90	129	0	Hypothyroidism	
19	70	F	Rheumatic heart disease (mitral stenosis and regurgitation)	19 d	130/92	140	0	Atrial fibrillation	Palpitation
	0	M	Atherosclerotic heart disease, hypertension	1 d	150/90	100	0	Chronic renal failure, congestive heart failure	Atrial fibrillation, PAT
21	53	M	Rheumatic heart disease (mitral regurgitation)	4 d	160/80	73	I		Atrial fibrillation
Mean ±SD CV	56 ±18				115 ±15/79 ±18	129 ±27			
NCV	68 ±14				137 ±24/80 ±21	116 ±31			
p value (CV vs NCV)	NS				<0·05 <0·05/NS	NS			

NYHA, New York Heart Association classification; LBBB, left bundle-branch block; PUO, pyrexia of unknown origin; PAT, paroxysmal atrial tachycardia; SD, standard deviation; NS, no significant difference.

of the presumed inaccuracies of this method. QRS and QT intervals were also measured and expressed as an average of 10 determinations. The QT interval was corrected for heart rate using the Bazett formula, $QTc = (QT/\sqrt{RR})$.[6]

Plasma procainamide levels were determined spectrophotometrically, using the method of Mark *et al.*,[7] within one minute of stopping the infusion. All 21 patients had standard M-mode echocardiograms for determination of maximum left atrial diameter at peak ventricular systole measured by the leading edge convention, using a Smith Kline Ekoline 20A ultrasonoscope interfaced with an Irex Continutrace strip chart recorder. Thyroid function studies (T_3 uptake and T_4 RIA) were obtained on all patients.

Variables of age, plasma procainamide level and dose, heart rate, and left atrial diameter were analysed by the unpaired t test; χ^2 analysis was used to compare the duration of atrial fibrillation between groups (converters vs non-converters). The paired t test was used to evaluate changes in QRS and QTc intervals within each group. An interval of 10 ms was arbitrarily chosen as the threshold of visual accuracy at 25 mm/s paper speed. Mean changes less than this value were considered to represent no change.

Results

Thyroid function was normal in all patients. In six of 21 patients, the cause of the atrial fibrillation could not be ascertained. Nine patients had atherosclerotic heart disease, seven had valvular heart disease, and five had systemic hypertension. Mitral valve disease was significantly more common in non-converters than in converters (6/12 vs 0/9, $p < 0{\cdot}05$). The incidence of idiopathic atrial fibrillation, atherosclerotic heart disease, or hypertension was not statistically different between converters and non-converters ($p > 0{\cdot}05$) (Table 1).

The duration of atrial fibrillation, as well as previous history of palpitation, documented atrial fibrillation, or other supraventricular arrhythmias are recorded in Table 1. All patients fitted the New York Heart Association classes 0, I, or II.

Table 2 *Determinants of conversion of atrial fibrillation by procainamide*

Case no.	*Dose*		*Plasma levels (μmol/l)*	*Reason for discontinuing infusion*	*Left atrial diameter (cm)*	*ΔQRS (%)*	*ΔQTc (%)*
	Total (mg)	*mg/kg*					
(A) Converters							
1	720	12·0	42·1	Conversion	3·6	NC	12
2	960	11·3	8·5	Conversion	2·7	–13	17
3	750	10·3	51·4	Conversion	—	NC	–8
4	1100	20·8	48·9	Conversion	3·2	—	—
5	840	14·7	41·6	Conversion	2·2	NC	3
6	690	10·0	8·1	Conversion	—	22	–11
7	990	17·1	38·3	Conversion	3·2	17	–5
8	990	12·8	17·4	Conversion	—	–12	–4
9	720	11·1	26·4	Conversion	3·2	NC	–4
						NS*	NS*
(B) Non-converters							
10	900	12·8	50·2	Full dose	—	11	8
11	900	15·8	45·5	Full dose	5·8	35	NC
12	990	16·2	—	Full dose	5·5	16	NC
13	990	13·4	113·9	Full dose	4·4	19	NC
14	990	10·9	44·6	Full dose	4·6	NC	—
15	990	13·2	—	Full dose	3·1	21	20
16	1000	20·8	32·3	Full dose	—	NC	12
17	990	12·4	49·3	Full dose	6·9	20	4
18	720	9·0	100·3	↓BP	5·1	—	16
19	630	10·5	46·8	↓BP	4·5	17	NC
20	570	8·4	—	↓BP	4·9	NC	3
21	990	14·8	48·9	Full dose	—	—	—
						p < 0·005*	p < 0·05*
Mean ±SD CV	862 ±150	13·3 ±3·6	31·5 ±16·6		3·0 ±0·6	2 ±12	0 ±9
NCV	888 ±156	13·1 ±3·5	59·1 ±32·3		4·9 ±1·0	14 ±14	6 ±7
p value (CV vs NCV)	NS	NS	< 0·05		< 0·005	< 0·05	NS

ΔQRS (%), per cent change in QRS duration; ΔQTc (%), per cent change in corrected QT interval; NC, no change; SD, standard deviation; NS, no significant difference.

* Comparison of mean changes before and after procainamide administration.

Initial ventricular rates varied between 70 and 170/min; initial blood pressures ranged from 90/70 to 176/120 mmHg.

Conversion to sinus rhythm occurred in nine patients. Twelve patients did not convert (Table 2). Hypotension necessitating discontinuation of infusion occurred in three non-converters, all of whom recovered spontaneously without specific treatment. The remaining nine patients who failed to convert to sinus rhythm received the maximum dose as defined previously. In the nine converters sinus rhythm was established at a mean dose of 862 ±150 mg (13·3 ±3·6 mg/kg), with a range of 690 to 1100 mg, at a mean plasma level of 31·5 ±16·6 µmol/l (7·4 ±3·9 µg/ml). There were no significant differences between converters and non-converters with respect to age, initial ventricular rates, initial QRS or QTc intervals, total dose of procainamide, or dose per kg body weight.

Non-converters achieved significantly higher mean plasma levels of procainamide, 59·1 ±32·3 µmol/l versus 31·5 ±16·6 µmol/l (13·9 ±7·6 µg/ml versus 7·4 ±3·9 µg/ml, $p < 0.05$) at similar doses per kg (13·1 ±3·5 mg/kg versus 13·3 ±3·6 mg/kg) (Fig. 1). Mean QRS and QTc intervals were not altered significantly in converters; these intervals were prolonged significantly, however, in non-converters ($p < 0.005$ and $p < 0.05$, respectively). The duration of atrial fibrillation and the mean left atrial diameter in converters were significantly less than those of non-converters ($p < 0.05$, and $p < 0.005$, respectively) (Table 1 and Fig. 2).

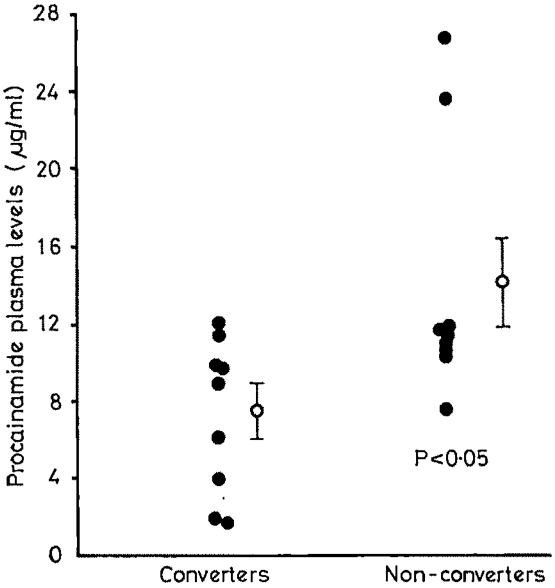

Fig. 1 *Relation between procainamide plasma levels and the tendency for conversion of atrial fibrillation to sinus rhythm during intravenous infusion. Closed circles represent plasma values for individual patients at the discontinuation of infusion. Open circles represent mean values with standard errors of means for both subgroups. Patients who did not convert to sinus rhythm had significantly higher plasma levels of the drug. Plasma levels were not available in three non-converters. To convert plasma levels to SI units, ie to µmol/l, multiply by 4·25.*

Discussion

The use of intravenous procainamide for the treatment of both ventricular extrasystoles and supraventricular arrhythmias, including atrial fibrillation, is, of course, not new.[7–10] The frequency of toxic manifestations, such as depression of cardiac output and blood pressure, vascular collapse, depression of cardiac impulse formation and conduction, prolongation of the QRS and QT intervals, and induction of ventricular arrhythmias precipitated by this route of administration, has been recognised previously.[11] In most instances, however, toxicity has occurred at infusion rates of 100 mg or more per minute.[11–13] It is likely that at these high

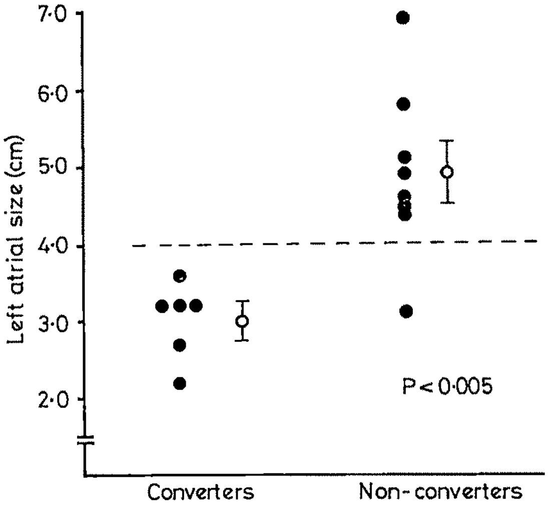

Fig. 2 *Relation between left atrial diameter measured by M-mode echocardiography and the tendency for conversion of atrial fibrillation to sinus rhythm. Meaning of symbols as in Fig. 1. Note that all patients with normal left atrial dimensions converted, except for one patient in whom atrial fibrillation was present for three months. Left atrial diameters were not obtainable in three patients from each subgroup.*

infusion rates, adequate drug distribution did not take place.[14] Though toxic manifestations have been reported with infusion rates of 25 mg/min in patients with acute or suspected myocardial infarction, in only two of 42 cases was it necessary to discontinue the infusion, and in both cases plasma levels of procainamide were in the therapeutic range.[15] It is generally accepted, therefore, that infusion rates of 25 to 50 mg per minute are safe and are accompanied by a low incidence of toxicity.[11 16] Though the presence of significant underlying heart disease also may predispose to toxicity,[17 18] possibly as a result of altered pharmacokinetics relating to different distribution characteristics, this feature was unlikely to be important in our patients who were in New York Heart Association class II or less.

An infusion rate of 30 mg/min produced conversion to sinus rhythm in nine patients with normal left atrial diameters at a time when plasma concentrations of procainamide were of the order of 29·7 µmol/l (7 µg/ml); in these patients, no significant alterations in the QRS or QTc intervals were noted. This was in contrast to the patients who did not convert despite higher plasma concentrations of the drug, in whom significant QRS and QTc prolongation were observed ($p < 0·005$ and $p < 0·05$, respectively). The fact that nonconverters had significantly higher plasma levels of procainamide at similar doses per kg of body weight when compared with converters is unexplained. Such differences, however, are not accounted for readily by differences in volumes of distribution, since the haemodynamic status, determined clinically, was similar in both patient subgroups. Though a majority of the plasma levels achieved in both subgroups was above the recommended therapeutic range for the steady state, all but two levels, 113·9 µmol/l (26·8 µg/ml) in case 13 and 100·3 µmol/l (23·6 µg/ml) in case 18, are in agreement with previously reported values for the initial phase of rapid distribution after intravenous administration.[13]

That the mean dose of procainamide required for conversion was greater than the maximum recommended loading dose is not surprising since conversion of atrial arrhythmias has been known to require higher concentrations of procainamide than has conversion of ventricular arrhythmias.[19] That no patients converted at a dose of 10 mg/kg or less is surprising, however, and should be borne in mind when attempting to convert atrial fibrillation by this method.

In three of our patients (cases 18, 19, 20), it was necessary to discontinue drug administration at relatively low doses because of hypotension, before conversion to sinus rhythm could be achieved. In these patients hypotension could not be related to excessive drug administration, or to toxic plasma drug levels in one of them (case 19, plasma level 46·8 µmol/l (11·0 µg/ml)). A plasma drug level was not obtained in case 20 because of technical reasons, but in case 18 the procainamide plasma level of 100·3 µmol/l (23·6 µg/ml) and the degree of prolongation of the QTc interval (16%) were among the highest in the entire series. In these patients, decreases were recorded in both systolic and diastolic blood pressures, suggesting, as has been reported previously, that alterations in blood pressure resulting from procainamide are induced by myocardial depression,[11 18 20] and peripheral vasodilatation.[16] Alterations in blood pressure were not limited to these three patients, however, and, in fact, most converters manifested modest drops in both systolic and diastolic blood pressures just before conversion; no specific treatment was needed.

The duration of atrial fibrillation and the left atrial diameter are among the determinants of the likelihood for cardioversion by direct current countershock.[21] Since the tendency for spontaneous return to sinus rhythm also may be related to these variables, might the patients in the present study have converted spontaneously? If so, sinus rhythm would have been as likely as not to have been restored at inappropriately low doses of the drug. In fact, however, every converter required at least 10 mg/kg. In two patients, restoration of sinus rhythm occurred at plasma levels less than 17 µmol/l (4 µg/ml). Though these patients may have converted spontaneously, their elimination from the study group would not have appreciably altered the statistical analysis.

While our data indicate that procainamide is effective in converting atrial fibrillation to sinus rhythm, the mechanism of its action is not clear. As with quinidine, the major electrophysiological action of procainamide is to depress the fast response (class I effect) in cardiac muscle, leading to a lengthening of the effective refractory period. Other class I agents, however, such as lignocaine and mexiletine, which also prolong the effective refractory period in heart muscle, are ineffective in converting atrial fibrillation. Furthermore, it is known that pronounced shortening of the atrial action potential duration after vagal stimulation[22] or by the induction of thyrotoxicosis,[23] enhances the tendency to fibrillate. This fact is consistent with the observation that patients who relapse into atrial fibrillation after direct current countershock tend to have shorter atrial action potentials (assessed by intra-atrial suction electrodes) when compared with those who maintain stable sinus rhythm.[24] In this regard, it is interesting that amiodarone, which has a weak class I action but a pronounced tendency to prolong the action potential duration uniformly,[25] is often effective in restoring and maintaining sinus rhythm in patients with atrial fibrillation.[26]

Both procainamide and quinidine prolong the action potential duration in association with their potent class I actions. This combination of electrophysiological effects may contribute to their useful effects in atrial fibrillation. The fact that the QTc interval (reflecting ventricular repolarisation) was not prolonged by procainamide in patients who converted to sinus rhythm in the present series, does not negate the possibility that atrial repolarisation in these patients was delayed by the drug. Studies involving the measurement of atrial repolarisation time by intracavitary suction electrodes during procainamide conversion of atrial fibrillation will, therefore, be of much theoretical interest.

Whatever the precise mechanism of action of procainamide in converting atrial fibrillation to sinus rhythm, the clinical significance of the present study should be emphasised. Intravenous infusion of procainamide in patients who have no clinical evidence of significant left ventricular dysfunction appears to be effective, safe, and rapidly acting in the conversion to sinus rhythm of acute onset or paroxysmal atrial fibrillation. Potential converters can be identified readily by a history of recent onset atrial fibrillation, and by echocardiographic demonstration of normal left atrial size. Though no patient reverted to atrial fibrillation within 48 hours after conversion, no conclusions can be drawn regarding its long-term efficacy in maintaining sinus rhythm, since different antiarrhythmic drugs were used after conversion.

These results suggest that intravenous procainamide may be infused without a predetermined dose limit and discontinued either with conversion of atrial fibrillation or with the appearance of adverse reactions. This form of treatment may be superior to more conventional methods of conversion currently employed. If echocardiography is not available, we still advocate a trial of procainamide because of its simplicity and low morbidity.

References

1 Hoffman BF. The action of quinidine and procainamide on single fibres of dog ventricle and specialized conducting systems. *Ann Acad Bras Cienc* 1958; **29:** 365.

2 Bigger JT Jr. Arrhythmias and antiarrhythmic drugs. *Adv Intern Med* 1972; **18:** 251–81.

3 Singh BN. Rational basis of antiarrhythmic therapy: the clinical pharmacology of commonly used antiarrhythmic drugs. *Angiology* 1978; **29:** 206–42.

4 Rosen MR, Hoffman BF. Mechanisms of action of antiarrhythmic drugs. *Circ Res* 1973; **32:** 1–8.

5 Cranefield PF, Wit AL, Hoffman BF. Genesis of cardiac arrhythmias. *Circulation* 1973; **47:** 190–204.

6 Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920; **7:** 353–70.

7 Mark LC, Kayden HJ, Steele JM, *et al.* The physiologic disposition and cardiac effects of procaine amide. *J Pharmacol Exp Ther* 1951; **102:** 5–15.

8 McCord MC, Taguchi JT. A study of the effect of procaine amide hydrochloride on supraventricular arrhythmias. *Circulation* 1951; **4:** 387–93.

9 Miller G, Weinberg SL, Pick A. The effect of procaine amide (Pronestyl) in clinical auricular fibrillation and flutter. *Circulation* 1952; **6:** 41–50.

10 Pascale LR, Bernstein LM, Schoolman HM, Foley EF. Intravenous procaine amide in the treatment of cardiac arrhythmias. *Am Heart J* 1954; **48:** 110–22.

11 Bigger JT Jr, Heissenbuttel RH. The use of procaine amide and lidocaine in the treatment of cardiac arrhythmias. *Prog Cardiovasc Dis* 1969; **11:** 515–34.

12 Berry K, Garlett EL, Bellet S. Gefter WI. The use of Pronestyl in the treatment of ectopic rhythms: treatment of 98 episodes in 78 patients. *Am J Med* 1951; **11:** 431–41.

13 Koch-Weser J, Klein SW. Procainamide dosage schedules, plasma concentrations, and clinical effects. *JAMA* 1971; **215:** 1454–60.

14 Zapata-Díaz J, Cabrera E, Méndez R. An experimental and clinical study on the effects of procaine amide (Pronestyl) on the heart. *Am Heart J* 1952; **43:** 854–70.

15 Karlsson E. Procainamide and phenytoin: comparative study of their antiarrhythmic effects at apparent therapeutic plasma levels. *Br Heart J* 1975; **37:** 731–40.

16 Koch-Weser J. Clinical application of the pharmacokinetics of procaine amide. *Cardiovasc Clin* 1974; 63–75.

17 McClendon RL, Hansen WR, Kinsman JM. Hemodynamic changes following procaine amide administered intravenously. *Am J Med Sci* 1951; **222:** 375–81.

18 Harrison DC, Sprouse JH, Morrow AG. The antiarrhythmic properties of lidocaine and procaine amide. *Circulation* 1963; **28:** 486–91.

19 Schaffer AI, Steinman R, Scherf D. Intravenous procaine: its effect on the human electrocardiogram and on cardiac arrhythmias. *Cardiologia* 1950; **16:** 342–53.

20 Giardina EV, Heissenbuttel RH, Bigger JT Jr. Intermittent intravenous procaine amide to treat ventricular arrhythmias. *Ann Intern Med* 1973; **78:** 183–93.

21 Henry WL, Morganroth J, Pearlman AS, *et al.* Relation between echocardiographically determined left atrial size and atrial fibrillation. *Circulation* 1976; **53:** 275–9.

22 Burn JH. The cause of fibrillation. *Br Med J* **i:** 1960; 1379–84.

23 Freedberg AS, Papp JG, Vaughan Williams EM. The effect of altered thyroid state on atrial intracellular

potentials. *J Physiol (Lond)* 1970; **207:** 357–69.
24 Olsson SB, Cotoi S, Varnauskas E. Monophasic action potential and sinus rhythm stability after conversion of atrial fibrillation. *Acta Med Scand* 1971; **190:** 381–7.
25 Singh BN, Vaughan Williams EM. The effect of amiodarone, a new anti-anginal drug, on cardiac muscle. *Br J Pharmacol* 1970; **39:** 657–67.
26 Olsson SB, Brorson L, Varnauskas E. Class 3 antiarrhythmic action in man. Observations from monophasic action potential recordings and amiodarone treatment. *Br Heart J* 1973; **35:** 1255–9.

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Detection of persistent ductus in hypoplastic left heart syndrome by contrast echocardiography

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SUMMARY A patient with hypoplastic left heart syndrome was studied using contrast echocardiography after peripheral venous injection of dextrose. The combination of the parasternal and suprasternal approach allowed for identification of the right ventricular cavity, excluded the presence of right-to-left intracardiac shunts, and established normal ventriculoarterial connections.

From the abdominal approach, the abdominal aorta was identified as an echo-free space corresponding to this structure in position, which became opacified after peripheral injection of dextrose into the left-hand vein.

In view of the suprasternal and parasternal findings opacification of the abdominal aorta could only have occurred in the presence of a pulmonary artery to descending aorta shunt through a persistent ductus arteriosus.

Echocardiography is a reliable method for establishing the diagnosis of the hypoplastic left heart syndrome, and has the advantage of avoiding cardiac catheterisation in sick newborn babies.[1 2]

The echocardiographic detection of a big right ventricular cavity in the presence of a small left ventricular cavity and aortic root, together with the hypoplastic or absent mitral valve, has been taken as diagnostic of the syndrome.[3 4 5]

Peripheral venous injection of dextrose as an ultrasonic indicator has been used in the echocardiographic detection of right-to-left shunts,[6] and as a complementary method in the echocardiographic assessment of ventriculoarterial connections.[7]

The purpose of this paper is to present the characteristic filling patterns obtained from the parasternal, suprasternal, and abdominal approaches in this condition using peripheral venous injections of 5 per cent dextrose as ultrasonic indicator.

Case report

A 24-hour-old baby who had been born at term and weighed 2850 g was admitted to hospital in severe heart failure. On clinical examination there was dyspnoea, tachypnoea, and subcostal recession. The infant was pale with minimal central cyanosis. The peripheral pulses were slight but palpable, and the blood pressure in the four limbs was 40 mmHg by the flush method. There was right ventricular hypertrophy clinically, and on auscultation the first heart sound was loud, and the second heart sound was also loud and single. A pansystolic murmur grade 3/6 was heard at the left sternal edge, and a third heart sound was present at the apex. The liver was 4 cm below the costal margin. The electrocardiogram showed sinus rhythm with a heart rate of 150 per minute, and right atrial and right ventricular enlargement. The frontal axis was +130°. *X*-ray film of the chest showed cardiomegaly with a cardiothoracic ratio of 65 per cent, plethoric lung fields, and a narrow pedicle.

Echocardiography from the parasternal views showed a large right ventricular cavity (14·7 mm), a small left ventricular cavity 14 mm, and a small aortic root, 5·2 mm. The left atrium was enlarged 12 mm, and the pulmonary artery was also enlarged at 11·5 mm diameter. The four valves of the heart were visualised in the standard way.[8] The mitral valve was very small, though two leaflets could be seen. The aortic valve was visualised as a collection of thick echoes within the aortic root. The pulmonary valve was large and showed several of the features indicative of pulmonary hypertension.[9] The tricuspid valve was normal.

An intravenous cannula was fixed into a vein on the back of the baby's left hand, and peripheral injections of 5 per cent dextrose were made. From the parasternal view, after the injection, the right ventricle was completely opacified defining the interventricular septal wall, and the left ventricle remained free of contrast (Fig. 1B).

Slight angulation towards the aortic root and left atrium allowed the small aortic valve and big pulmonary artery to be visualised. Contrast injection opacified only the anterior great artery. The transducer was then placed in the suprasternal notch and the aortic arch, pulmonary artery, and left atrium were located.[10] The aortic arch was smaller than the pulmonary artery, 2·5 mm diameter as against 10 mm diameter. After peripheral venous injection only the pulmonary artery was opacified.

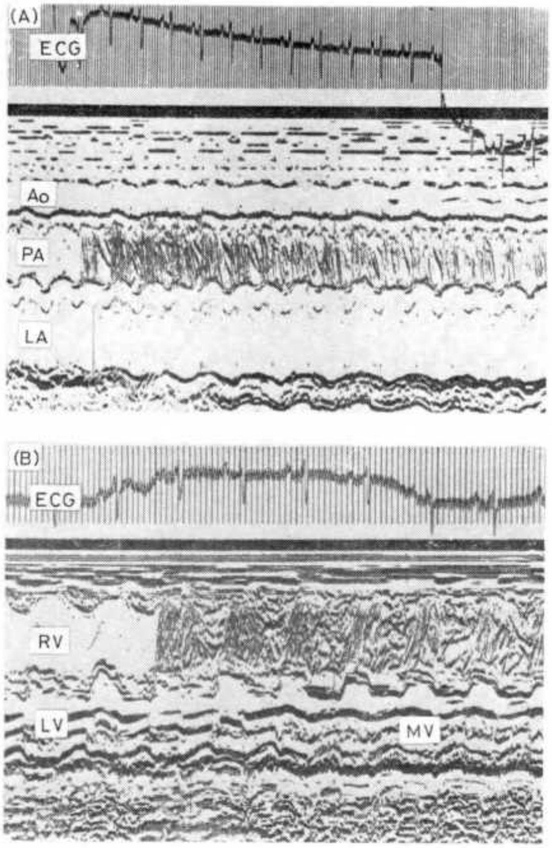

Fig. 1 (A) *Echocardiogram obtained from the suprasternal view. The aorta (Ao), the pulmonary artery (PA), and the left atrium (LA) are seen in the same echocardiographic plane. After peripheral venous injection of contrast, only the PA is opacified, suggesting that the ventriculoarterial connections are normal, with no evidence of a right-to-left intracardiac shunt.*
(B) *This echocardiogram has been recorded from the parasternal approach. The right ventricle (RV) and the left ventricle (LV) are seen in the same cut. After injection of 5 per cent dextrose into the baby's hand only the RV is opacified. No right-to-left shunt is detected. The mitral valve (MV) is visualised as a hypoplastic valvular structure.*

The combination of these two approaches excluded a right-to-left intracardiac shunt, and established a normal ventriculoarterial connection.[7]

The transducer was then placed in the abdomen to localise the abdominal aorta, and after peripheral venous injection, a small posterior echo-free space was opacified (Fig. 2). There was cyclical opacification after contrast injection, the contrast being more intense in systole than in diastole. The injection was repeated three times, with identical results, and the structure was therefore taken to represent the abdominal aorta filling through a persistent ductus arteriosus from the pulmonary artery, which in turn received its contrast directly from the heart. From previous experience with the technique the cyclical opacification eliminated the possibility that this was the inferior vena cava or other great vein.[11]

Unfortunately, 20 hours after the investigation the baby died before cardiac catheterisation was done.

At necropsy the right atrium was large with an intact atrial septum. It connected with a dilated right ventricle through a normal tricuspid valve and from this ventricle a big pulmonary artery arose. There was a persistent ductus arteriosus

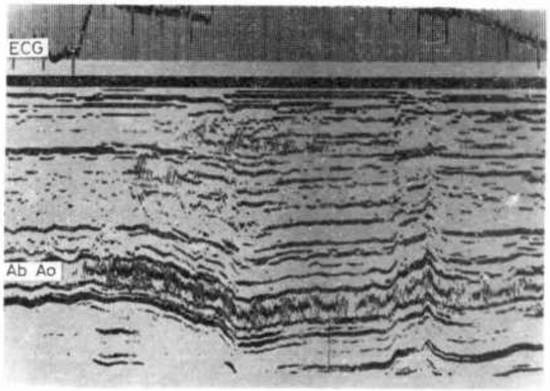

Fig. 2 *Echocardiogram performed from the baby's abdomen; linear echoes are visualised. After peripheral left-hand injection, opacification of the abdominal aorta (Ab Ao) occurs. Intense systolic opacification is followed by slight diastolic attenuation. In the absence of an intracardiac right-to-left shunt, this filling pattern represents a pulmonary artery-descending aorta shunt in the presence of a persistent ductus arteriosus.*

with a diameter of 3 mm. The left atrium was normal, and received all four pulmonary veins. The mitral valve was hypoplastic and had two well-defined anterior and posterior leaflets, with two small papillary muscles. The left ventricle was hypoplastic (diameter 16 mm) with thick walls and pronounced endocardial fibroelastosis, and gave rise to a bicuspid hypoplastic aortic valve and a small ascending aorta with a diameter of 6 mm. The coronary arteries were normal though the aortic arch was small, 3·5 mm. There was evidence of heart failure.

Discussion

Echocardiography is a reliable method of defining intracardiac anatomy. In sick neonates with hypoplastic left heart syndrome, echocardiography can give a definitive diagnosis without recourse to cardiac catheterisation.[1 2]

However, when only one atrioventricular valve is visualised echocardiographically, it is often difficult to differentiate the hypoplastic left heart syndrome from other conditions with one functional atrioventricular valve. On occasions the interventricular septum can only be reliably identified using contrast studies. Therefore, in these children there are three reasons for using contrast echocardiography before catheterisation is done: firstly, to define the limits of cardiac cavities, which may be obscure; secondly, to detect right-to-left intracardiac shunts; and thirdly, to establish ventriculoarterial connections.[7] In this case the views from the parasternal approach showed a big right ventricle and a small left ventricle. Contrast echocardiography delineated the right ventricular walls and showed absence of right-to-left shunts at intracardiac level (Fig. 1B). The suprasternal approach showed the opacification of the pulmonary artery only, from which we deduced that ventriculoarterial connections were normal (Fig. 1A).

When the transducer was placed on the abdomen several linear echoes were seen but there was not enough definition to identify the abdominal aorta with certainty. However, after peripheral venous injections into the left hand, contrast echoes filled the space between the two linear echoes (Fig. 2).

This pattern of filling, shown by peripheral injections of dextrose, and using the parasternal and the suprasternal transducer positions, indicated that the contrast injected into the left hand could only reach the abdominal aorta through a right-to-left shunt via a persistent ductus arteriosus.

The use of different transducer positions together with peripheral contrast echocardiography can increase diagnostic accuracy in complex cardiac anomalies; in the absence of intracardiac right-to-left shunts the opacification of the abdominal aorta demonstrates the presence of a persistent ductus arteriosus with reverse ductal shunting.

References

[1] Meyer RA, Kaplan S. Echocardiography in the diagnosis of hypoplasia of the left or right ventricles in the neonate. *Circulation* 1972; **46:** 55–64.

[2] Godman MJ, Tham P, Langford Kidd BS. Echocardiography in the evaluation of cyanotic newborn infant. *Br Heart J* 1974; **36:** 154–66.

[3] Chesler E, Joffe HS, Vecht R, Beck W, Schrire V. Ultrasound cardiography in single ventricle and the hypoplastic left and right heart syndromes. *Circulation* 1970; **42:** 123–9.

[4] Lundström N-R. Ultrasound cardiographic studies of the mitral valve region in young infants with mitral atresia, mitral stenosis, hypoplasia of the left ventricle, and cor triatriatum. *Circulation* 1972; **45:** 324–34.

[5] Farooki ZQ, Henry JC, Green EW. Echocardiographic spectrum of the hypoplastic left heart syndrome. A clinicopathologic correlation in 19 new borns. *Am J Cardiol* 1976; **38:** 337–43.

[6] Valdés-Cruz LM, Pieroni DR, Roland JA, Vaghese BJ. Echocardiographic detection of intercardiac right to left shunts following peripheral vein injections. *Circulation* 1976; **55:** 558–62.

[7] Mortera C, Hunter S, Tynan M. Diagnosis of ventriculoarterial discordance (transposition of the great arteries) by contrast echocardiography. *Br Heart J* 1977; **39:** 844–46.

[8] Solinger R, Elbl F, Minhas K. Deductive echocardiographic analysis in infants with congenital heart disease. *Circulation* 1974; **50:** 1072–96.

[9] Weyman AE. Pulmonary valve echo motion in clinical practice. *Am J Med* 1977; **62:** 843–55.

[10] Goldberg BB. Ultrasonic measurement of the aortic arch, right pulmonary artery and left atrium. *Radiology* 1971; **101:** 383–90.

[11] Mortera C, Hunter S, Tynan M. Contrast echocardiography and the suprasternal approach in infants and children. *Eur J Cardiol* 1979; **9:** 437–54.

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Br Heart J 1980; **44:** 599–601

Echocardiographic findings of floating thrombus in left atrium

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SUMMARY We describe the M-mode and two-dimensional echocardiographic findings of a floating thrombus in the left atrium. Though the features resembled those of pedunculated left atrial myxoma, two-dimensional echocardiography was helpful in differentiating between thrombus and myxoma in the left atrium.

As is well known, thromboembolism is one of the most severe complications of mitral stenosis. Echocardiography has been used as a non-invasive tool for detecting thrombi in the left atrium.[1–3] To our knowledge, however, there has been only one brief report on the M-mode echocardiographic findings of a floating thrombus.[4] In this report, the M-mode and two-dimensional echocardiographic findings of a floating thrombus are presented in detail.

Case report

A 42-year-old man with mitral stenosis was referred to us on 8 July 1978 for echocardiographic evaluation. He experienced successive episodes of thromboembolism of the femoral artery, superior mesenteric artery, and cerebral artery during the previous few months. The patient was in atrial fibrillation and had been treated with digitalis. Physical examination, chest *x*-ray film, and phonocardiography showed that he had moderately severe mitral stenosis. A tumour plop sound was not detected by phonocardiography.

M-MODE ECHOCARDIOGRAPHIC FINDINGS

The echoes of a floating thrombus, which was confirmed by surgical operation as described below, were detected posterior to the anterior mitral leaflet during diastole in some cardiac cycles. The area behind the mitral valve was relatively free of echoes during systole and the initial phase of diastole. The appearance of these echoes was not always regular in timing, but their disappearance was rapid at every end-diastole (Fig. 1). The echoes of a floating thrombus behind the anterior mitral leaflet appeared as band-like echoes; this thrombus also produced a fuzzy appearance in the body of the left atrium. Mural thrombus could not be detected in the left atrium echocardiographically. These echocardiographic findings partially resembled those of pedunculated left atrial myxoma, but with floating thrombus there seems to be no regularity in the appearance of the echoes or synchronisation with cardiac cycles.

TWO-DIMENSIONAL ECHOCARDIOGRAPHIC FINDINGS

Two-dimensional echocardiograms of the long cardiac axis are presented in Fig. 2. All four polaroid films were obtained at end-diastole. The echoes of a floating thrombus were in the body of the left atrium and posterior to the mitral valve, and were variable in size and position in each cycle. The echogenic tissues seemed to be floating freely within the left atrial cavity and sometimes disappeared from the long cardiac axis. These findings suggested that the thrombus was not attached to the left atrial wall or to the mitral valve. The largest thrombus echoes were $3{\cdot}5 \times 1{\cdot}5$ cm.

CINEANGIOGRAPHIC AND SURGICAL FINDINGS

Pulmonary artery injection of contrast medium was performed, with follow-through to the left atrium. A small mass could be visualised floating in the left atrium.

At operation (13 July 1978), a thrombus measuring $3{\cdot}7 \times 1{\cdot}6 \times 1{\cdot}5$ cm was found in the left atrium, unattached to any part of the wall or to the mitral valve. There was no mural thrombus in the body and appendage of the left atrium. The mitral leaflets were moderately thickened and fused, the mitral orifice measuring 2·0 cm in diameter. The thrombus was removed from the left atrium and mitral commissurotomy was performed.

Discussion

Thrombus in the left atrium is sometimes found in patients with mitral stenosis. Though echocardiography has been used for detecting thrombi, they are difficult to visualise with standard techniques because most are small and occur in the left atrial appendage.[3] Occasionally, a large thrombus may be layered and adherent to the posterior left atrial wall, and produce fuzzy echoes or a band of linear echoes, which are difficult to differentiate from the signals emanating from the left atrial posterior wall.[4]

On the other hand, echocardiographic findings of a floating thrombus within the left atrial cavity may be characteristic, as shown in this case. The echoes of the floating thrombus were detected as band-like echoes posterior to the mitral valve and as fuzzy echoes in the body of the left atrium by M-mode echocardiography. In addition, most of these echoes behind the mitral valve appeared at diastole and disappeared rapidly at end-diastole, as do the echoes of a pedunculated left atrial myxoma.[5] These findings were considered to be characteristic of the random motions of a floating thrombus in the left atrium, not synchronised with cardiac cycles.

Using two-dimensional echocardiography, it is easily possible to confirm the free movement of a floating thrombus within the left atrial cavity, and to estimate the variation in size and position which are not coincident with the cardiac cycles. These findings partially resemble those of left atrial myxoma.[6] Though the motions of echoes of pedunculated left atrial myxoma may be regular and associated with cardiac cycles, there was no regularity in motions in the case of a floating thrombus. Two-dimensional echocardiography was useful in differentiating the motions of such abnormal echoes in the left atrium.

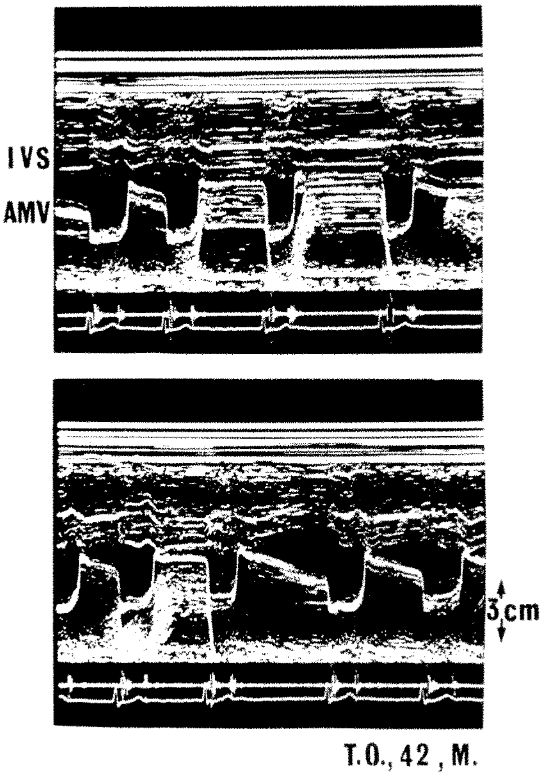

Fig. 1 *The band-like echoes of a floating thrombus were detected posterior to the anterior mitral valve during diastole in some cardiac cycles. Their appearance was not always regular in timing, and these echoes disappeared rapidly at end-diastole. IVS, interventricular septum; AMV, anterior mitral valve.*

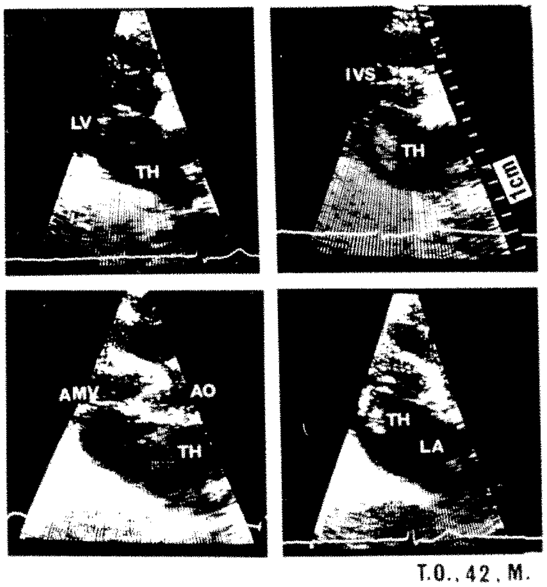

Fig. 2 *Two-dimensional echocardiograms of the long cardiac axis are shown. All four polaroid films were obtained at end-diastole. Thrombus echoes (TH) were in the body of the left atrium and posterior to the mitral valve. Their sizes and positions were variable.*

We present the M-mode and two-dimensional echocardiographic findings of a floating thrombus in the left atrium. Though echocardiographic detection of thrombi is usually difficult, it is relatively easy to visualise a thrombus if it is floating freely within the left atrial cavity, as was confirmed in this case. Furthermore, two-dimensional echocardiography is useful in detecting the motions of a floating thrombus.

We acknowledge the help of Drs Hamao Ijichi, Kohichi Ohga, Kimimasa Tamari, Takeshi Kakiuchi, Toshimitsu Watanabe, and Yukio Torii.

References

[1] Segal BL, Likoff W, Kingsley B. Echocardiography: clinical application in mitral stenosis. *JAMA* 1966; **195:** 161–6.
[2] Tallury MD, DePasquale NP. Ultrasound cardiography in the diagnosis of atrial thrombus. *Chest* 1971; **59:** 501–3.
[3] Spangler RD, Okin JT. Echocardiographic demonstration of a left atrial thrombus. *Chest* 1975; **67:** 716–8.
[4] Feigenbaum H. *Echocardiography*. 2nd ed. Philadelphia: Lea & Febiger, 1976: 248.
[5] Bass NM, Sharratt GP. Left atrial myxoma diagnosed by echocardiography, with observation on tumor movement. *Br Heart J* 1973; **35:** 1332–5.
[6] Kerber RE, Kelly, DH Jr, Gutenkauf CH. Left atrial myxoma. Demonstration by stop-action cardiac ultrasonography. *Am J Cardiol* 1974; **34:** 838–41.

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Br Heart J 1980; **44**: 602–3

Extreme tachycardia complicating the use of disopyramide in atrial flutter

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SUMMARY A 59-year-old man presented with atrial flutter and a 2:1 atrioventricular response, which, after intravenous disopyramide, became 1:1. A mechanism of slowed atrial flutter rate and improved atrioventricular nodal conduction, similar to that recognised with quinidine, is suggested.

Disopyramide is an antiarrhythmic drug which has pharmacological properties similar to quinidine[1 2] and a wide spectrum of efficacy. It has been advocated for the treatment of virtually all supraventricular tachyarrhythmias, including atrial flutter. With few exceptions it has been well tolerated, but dose-related anticholinergic side effects are occasionally troublesome. There has been a report of disopyramide toxicity complicated by ventricular tachycardia[3] but in the case reported here acute administration of disopyramide in normal doses to a patient with atrial flutter resulted in a life-threatening tachycardia. Similar responses have been previously associated with quinidine[4] and this occurrence with disopyramide is not unexpected.

Case history

A 59-year-old labourer presented with a three-week history of dyspnoea on exertion, palpitation, and ankle swelling. Four years previously he had been admitted to another hospital with similar symptoms and had been treated with cardioversion. His daily alcohol intake was in excess of 16 pints of beer; he smoked 40 cigarettes a day and had a 15-year history of chronic bronchitis. He had taken no drugs before admission.

On examination he was obese, plethoric, and undistressed. He had a regular tachycardia of 160 per minute, without a pulse deficit; the blood pressure was 165/120 mmHg. The jugular venous pressure was raised above the angle of the jaw; there was moderate dependent oedema and fine bilateral basal crepitations were present.

A 12 lead electrocardiogram showed atrial flutter with 2:1 atrioventricular block and a ventricular rate of 160 per minute (Fig. trace A), The chest *x*-ray film disclosed cardiomegaly and pulmonary venous congestion.

He was admitted to the coronary care unit. The arrhythmia failed to respond to carotid sinus massage and the Valsalva manoeuvre. Subsequently disopyramide phosphate was given by slow intravenous injection at a rate of 10 mg per minute. After the administration of 80 mg he developed short runs of atrial flutter with 1:1 atrioventricular conduction and a ventricular rate of 240 per minute with no change in QRS morphology. The infusion was discontinued. This rhythm (Fig. trace B) persisted, however, and he rapidly lost consciousness and had a *grand mal* convulsion. He was immediately cardioverted, initially unsuccessfully at 100 J followed by successful cardioversion at 200 J, with restoration of normal sinus rhythm at a rate of 90 per minute. There was prompt improvement in his perfusion and he regained consciousness shortly thereafter.

Further investigations confirmed that he was euthyroid. There was no clinical or echocardiographic evidence of valvular disease. Standard 12 lead electrocardiograms were within normal limits with no evidence of pre-excitation or anomalous atrioventricular conduction. His liver function tests were deranged with bilirubin 20 nmol/l (normal 2 to 17 nmol/l) and serum gamma glutaryl transferase 82 units/l (normal 10 to 55 units/l). These investigations were compatible with his excessive alcohol consumption and he was presumed to have an alcoholic cardiomyopathy.

Nine months after this episode he remains well,

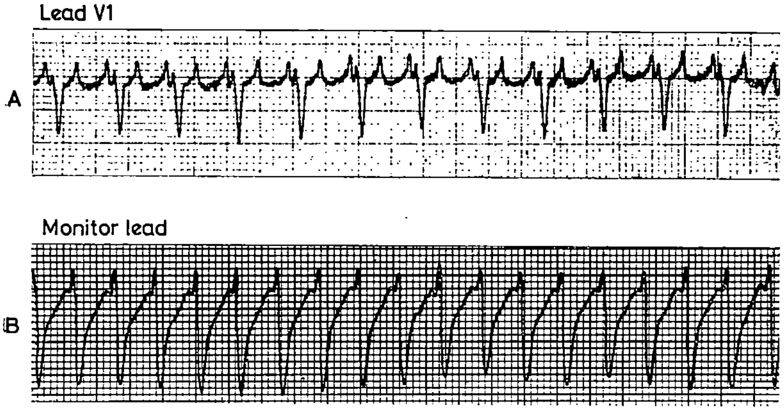

Fig. *Electrocardiogram: (*A*) shows atrial flutter with 2:1 atrioventricular conduction and ventricular rate 160 per minute; (*B*) after 80 mg disopyramide intravenously over eight minutes. The different QRS morphology is the result of the different electrocardiographic lead recorded.*

in atrial fibrillation, with a ventricular rate controlled on digoxin alone.

Comment

The effect of disopyramide on atrioventricular nodal conduction is variable, probably because of varying vagal tone, but enhancement of conduction occurs in some patients.[5] Recently it has been shown that intravenous disopyramide slows the atrial rate in patients in whom atrial flutter has been initiated by atrial pacing.[6] We believe that in our case the administration of disopyramide slowed the atrial flutter rate from 320 per minute to 270 per minute, while improving atrioventricular nodal conduction, thus allowing a 1:1 atrioventricular response. A similar electrophysiological mechanism is well recognised with quinidine[4] and before treating atrial flutter or atrial fibrillation with quinidine prior treatment with digoxin has been recommended to decrease atrioventricular node conduction time and to increase the degree of atrioventricular block, thus preventing a rapid ventricular response. Disopyramide and quinidine are very similar drugs so this complication with disopyramide is not unexpected. Like quinidine, therefore, we would advocate that disopyramide is contraindicated in the treatment of atrial flutter or atrial fibrillation unless atrioventricular conduction is slowed by prior treatment with digoxin or a beta-blocker. Atrial flutter is at times difficult to identify as the cause of supraventricular tachycardia so this possibility should be entertained before administering disopyramide indiscriminately for supraventricular tachyarrhythmias.

References

1 Hall RC, Brogden RN, Spreight TM, Avery GS. Disopyramide. A review of its pharmacological properties and therapeutic use in treating cardiac arrhythmias. *Drugs* 1978; **15:** 331–68.
2 Josephson ME, Caracta AR, Lau SH, Gallagher JJ, Damato AN. Electrophysiological evaluation of disopyramide in man. *Am Heart J* 1973; **86:** 771–80.
3 Meltzer RS, Robert EW, McMorrow M, Martin RP. Atypical ventricular tachycardia as a manifestation of disopyramide toxicity. *Am J Cardiol* 1978; **42:** 1049–53.
4 Laurence DR. *Clinical pharamacology.* 2nd ed. London: J & A Churchill, 1963: 334.
5 Befeler B, Castellanos A Jr, Wells DE, Vagueiro MC, Yeh BK. Electrophysiologic effects of the antiarrhythmic agent disopyramide phosphate. *Am J Cardiol* 1975; **35:** 282-7.
6 Camm J, Ward D, Spurrell RAJ. Response of paroxysmal atrial flutter to intravenous disopyramide phosphate and overdrive atrial pacing (abstract). *Br Heart J* 1979; **42:** 237.

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Br Heart J 1980; **44:** 604–5

Effect of intravenous propranolol on QT interval

Sir,

We read with interest the study of Milne *et al.* (*Br Heart J* 1980; **43:** 1–6) dealing with a new method to assess the effects of intravenous propranolol on QT interval and wish to comment on some aspects of their paper.

(1) The QT interval of the electrocardiogram can be interpreted only after correction for the cardiac cycle length. Bazett's formula is frequently used for this purpose and expressed as the symbol QTc: an absolute value of QTc exceeding 440 ms means prolongation.[1] Previous reports indicate that a prolonged QTc may represent a significant risk index for major cardiac arrhythmias in acute or healed myocardial infarction.[2, 3] On the other hand, antisympathetic drugs are used in such clinical situations and may help prevent sudden death.[4, 5] Propranolol,[6] alprenolol,[7] and bretylium tosylate[8] shorten the QTc interval and this may be how they reduce the incidence of major arrhythmias.

The conclusions drawn by Milne *et al.* do not apparently support this view.

(2) It is surprising however that such a relevant point is not supported by an unbiased statistical analysis.[9] Furthermore, when comparing (variance analysis) the QTc of all 15 patients with measurements obtained in sinus rhythm and during atrial pacing, before and after propranolol (0·1 mg/kg over three minutes) it is evident (see Table) that: (a) propranolol induces a marginally significant ($p<0{\cdot}065$) reduction of QTc when infused in patients in sinus rhythm; (b) the lengthening of QTc after propranolol during atrial pacing is statistically not significant; (c) there is a highly significant ($p<0{\cdot}00001$) lengthening induced by the proposed new method, irrespective of whether the drug was given.

Table *QTc before and after propranolol (mean±SD) in 15 patients*

$$QTc=\frac{QT}{\sqrt{RR}}\ (ms)$$

	Sinus rhythm		*Atrially paced*	
	Before	*After*	*Before*	*After*
	416 ±18	*401 ±23*	*485 ±39*	*498 ±40*
F=35 $p<0{\cdot}00001$	× × ×	× × ×	× × ×	× × ×
F=3·67 $p<0{\cdot}065$	× × ×	× × ×		
F=0·81 NS			× × ×	× × ×
F=38 $p<0{\cdot}00001$	× × ×		× × ×	
F=65 $p<0{\cdot}00001$		× × ×		× × ×

(3) While the method described by Milne *et al.* deserves to be validated in a larger and more homogeneous series, it does not seem that the suggested action of propranolol in prolonging the QT interval duration during atrial pacing is substantiated.

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References

1 Moss AJ, Schwartz, PJ. Sudden death and the idiopathic long Q-T syndrome. *Am J Med* 1979; **66:** 6–7.
2 Ahnve S, Lundman T, Shoaleh-Var M. The relationship between QT interval and ventricular arrhythmias in acute myocardial infarction. *Acta Med Scand* 1978; **204:** 17–9.
3 Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 1978; **57:** 1074–7.
4 Wilhelmsson C, Vedin JA, Wilhelmsen L, Tibblin G, Werkö L. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. Preliminary results. *Lancet* 1974; **ii:** 1157–60.
5 Multicentre International Study. Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. *Br Med J* 1975; **iii:** 735–40.
6 Stern S, Eisenberg S. The effect of propranolol (Inderal) on the electrocardiogram of normal subjects. *Am Heart J* 1969; **77:** 192–5.
7 Nyberg G, Vedin A, Wilhelmsson C. QT time in patients treated with alprenolol or placebo after myocardial infarction. *Br Heart J* 1979; **41:** 452–5.
8 Singer PA, Crampton RS, Bass NH. Familial Q-T prolongation syndrome. Convulsive seizure and paroxysmal ventricular fibrillation. *Arch Neurol* 1974; **31:** 64–6.
9 Glantz SA, Biostatistics: how to detect, correct and prevent errors in the medical literature. *Circulation* 1980; **61:** 1–7.

This letter was shown to Dr Milne and his colleagues who reply as follows:

Sir,

Puddu and his colleagues point out many of the difficulties in the interpretation of the QT interval, and of the changes of the QT interval occasioned by atrial pacing and by physiological or pharmacological manoeuvres. Though physiological changes in the QT interval can possibly be corrected for concomitant rate changes by the use of correction factors such as Bazett's formula, there is no evidence that changes of rate induced by atrial pacing or by drugs can be similarly corrected. Indeed the results of our research suggest that in the case of atrial pacing, in which rates were used which extended beyond the physiological range assessed by Bazett, simple hyperbolic correction was completely inaccurate as implied in paragraph 2c of the letter by Puddu and his colleagues.

In order to compensate for the bradycardia induced by propranolol, a comparison of pre- and post-propranolol QT intervals can be made by correcting both values for rate according to Bazett's formula. Alternatively, rate can be controlled by atrial pacing at identical frequencies both before and after drug administration. Our results indicated that, when using Bazett's correction the QTc usually shortened after propranolol, but when fixing the rate by atrial pacing, the QT tended to lengthen. As is pointed out by Puddu and colleagues, this result was not statistically significant.

These combined results suggest that one or other method is inappropriate and we are, as yet, prepared to accept that making comparisons at non-physiological atrial paced rates may lead to incorrect results. We are also very unsure, however, about the validity of assuming that Bazett's correction can be applied to pharmacologically induced changes of rate. Rickards *et al.*[1] confirm our belief that simple hyperbolic correction should be not applied to QT interval changes induced by atrial pacing. Their results, like ours, lead to the conclusion that Bazett's correction would seriously overestimate the QTc at atrial driven rates above 100 a minute.

We should also point out that the results of our work do not necessarily apply to the effects of rate changes or beta-blockade on the QT interval in abnormal repolarisation syndromes. The QT interval response to the imposition of an artificial rate, abnormal depolarisation sequence, or pharmacological intervention may be characteristically different from the results in our "normal" series.

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Reference

1 Rickards AF, Akhras F, Baron DW. Effects of heart rate on QT interval. In: Meere C, ed. *Proceedings of VIth world symposium on cardiac pacing*. Montreal: Laplante and Langevin, 1979. 2:7.

Br Heart J 1980; **44:** 606–7

Aortic root dissection

Sir,

Candell-Riera and co-workers recently reported early systolic closure of the aortic valve in two cases with aortic root dissection.[1] They state that this partial closure of the aortic valve has also been observed in discrete subaortic stenosis, mitral regurgitation, and ventricular septal defect.

Apart from these conditions, partial closure of the aortic valve has been shown in hypertrophic cardiomyopathy with and without obstruction[2] and in ruptured right coronary sinus of Valsalva aneurysm into the right ventricle.[3] The haemodynamic situation in the latter condition may be similar to that in case 1 of the report by Candell-Riera and his colleagues in which the aortic root dissection ruptured into the pericardial and pleural spaces.

In the echocardiogram of this case (Fig. 1B) a structure is identified by a lower, large horizontal arrow, as the external layer of the aorta. The motion of this structure, however, appears to be out of phase with that of the anterior aortic root. The patient had a pericardial effusion and I wonder whether it is the left atrial wall which is labelled and the echo-free space posterior is a pericardial effusion behind the left atrium.[4] A continuous sweep recording from the aortic root through the mitral valve to the left ventricular plane might have clarified the situation.

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References

1 Candell-Riera J, Garcia del Castillo H, Rius J. Aortic root dissection. Another cause of early systolic closure of the aortic valve. *Br Heart J* 1980: **43:** 579–81.

2 Doi YL, McKenna WJ, Gehrke J, Oakley CM, Goodwin JF. M-mode echocardiography in hypertrophic cardiomyopathy: diagnostic criteria and prediction of obstruction. *Am J Cardiol* 1980; **45:** 6–14.

3 Johnson ML, Warren SG, Waugh RA, Kisslo JA, Sabiston DC, Lester RG. Echocardiography of the aortic valve in non-rheumatic left ventricular outflow tract lesions. *Radiology* 1974; **112:** 677–84.

4 Greene DA, Kleid JJ, Naidu S. Unusual echocardiographic manifestation of pericardial effusion. *Am J Cardiol* 1977; **39:** 112–5.

This letter was shown to Dr Candell-Riera who replies as follows:

Sir,

In our two reported cases of aortic root dissection as well as in a more recent one that we have had the opportunity of seeing, the partial systolic aortic closure recorded in the echocardiogram was very premature (less than 0·05 s from the opening point). For that reason we did not discuss the differential diagnosis with hypertrophic cardiomyopathy, since in the latter condition the closure of the aortic leaflets occurs later (at $0{\cdot}14 \pm 0{\cdot}04$ s from the opening point) as Krajcer *et al.*[1] have shown. Accordingly, Doi *et al.*[2] have referred to this closure in the obstructive and non-obstructive hypertrophic cardiomyopathy as being "mid-systolic" rather than "early systolic".

We agree with Dr Doi that this early systolic closure of the aortic leaflets can be seen in a ruptured right coronary sinus of Valsalva into the right ventricle and have recently seen such a case. We have also observed this sign in a case of constrictive pericarditis, in aortic regurgitation with severe aortic root dilatation without dissection, and in situations of severe low cardiac output. Moreover, Krueger *et al.*[3] have pointed out the presence of a slight systolic aortic partial closure in normal subjects.

As we mention in our paper, pericardial effusion posterior to the left atrium can be confused with dissection of the posterior wall of the aorta. This possibility, which Dr Doi refers to in relation to Fig. 1B of our report, can be ruled out, not only by the continuous sweep recording from the aortic root to the left ventricle, but also by aortography. In the left lateral projection of the angiogram the false lumen of the aorta was seen in the anterior as well as in the posterior wall, thus coinciding with the echocardiographic recordings of the false lumen in size and location.

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Barcelona, Spain.

References

1 Krajcer Z, Orzan F, Pechacek LW, García E, Leachman RD. Early systolic closure of the aortic valve in patients with hypertrophic subaortic stenosis and discrete subaortic stenosis. Correlation with preoperative and postoperative hemodynamics. *Am J Cardiol* 1978; **41:** 823–9.

2 Doi YL, McKenna WJ, Gehrke J, Oakley CM, Goodwin JF. M-mode echocardiography in hypertrophic cardiomyopathy: diagnostic criteria and prediction of obstruction. *Am J Cardiol* 1980; **45:** 6–14.

3 Krueger SK, French JW, Forker AD, Caudill CC, Popp RL. Echocardiography in discrete subaortic stenosis. *Circulation* 1979; **59:** 506–13.

Notices

Br Heart J 1980; **44:** 608

The International Society of Mechanocardiography (ISM)

This society is organising the First European Conference on Mechanocardiography in Leuven, Belgium, on 9–11 April 1981.

For further information apply to: Dr A E Aubert, Secretary ISM, Cardiology Department, St. Raphael University Hospital, B-3000 Leuven, Belgium.

Paediatric cardiology

The next conference on Paediatric Cardiology will be held in London at the Royal College of Obstetricians and Gynaecologists on 16–18 September 1981.

Details from: Conference Services Ltd, 3 Bute Street, London SW7.

The Fifth World Conference on Smoking and Health

This will be held in Winnipeg, Canada, from 10 to 15 July 1983.

For further information apply to: Fifth World Conference on Smoking and Health, P.O. Box 228, Station B, Ottawa, Ontario, K1P 6C4, Canada.

International Conference on Non-invasive Techniques

This conference, sponsored by American College of Chest Physicians, Western India Chapter, will be held in Bombay, 6 to 8 December 1981.

For further information apply to: Dr Ashok T Tulpule, Secretary-General, International Conference on Non-Invasive Techniques, Patel Chamber, French Bridge, Bombay 400 007, India.

Sir Thomas Lewis (1881-1945): an historical perspective

A one-day symposium on this theme will be held at the Wellcome Institute for the History of Medicine on 24 April 1981. Speakers will include Dr Arthur Hollman, Dr John Honour, Dr Dennis Krikler, Sir Edward Pochin, Professor H A Snellen, and Sir Edward Wayne.

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Further details from Dr C J Lawrence, Wellcome Institute for the History of Medicine, 183 Euston Road, London NW1 2BP.

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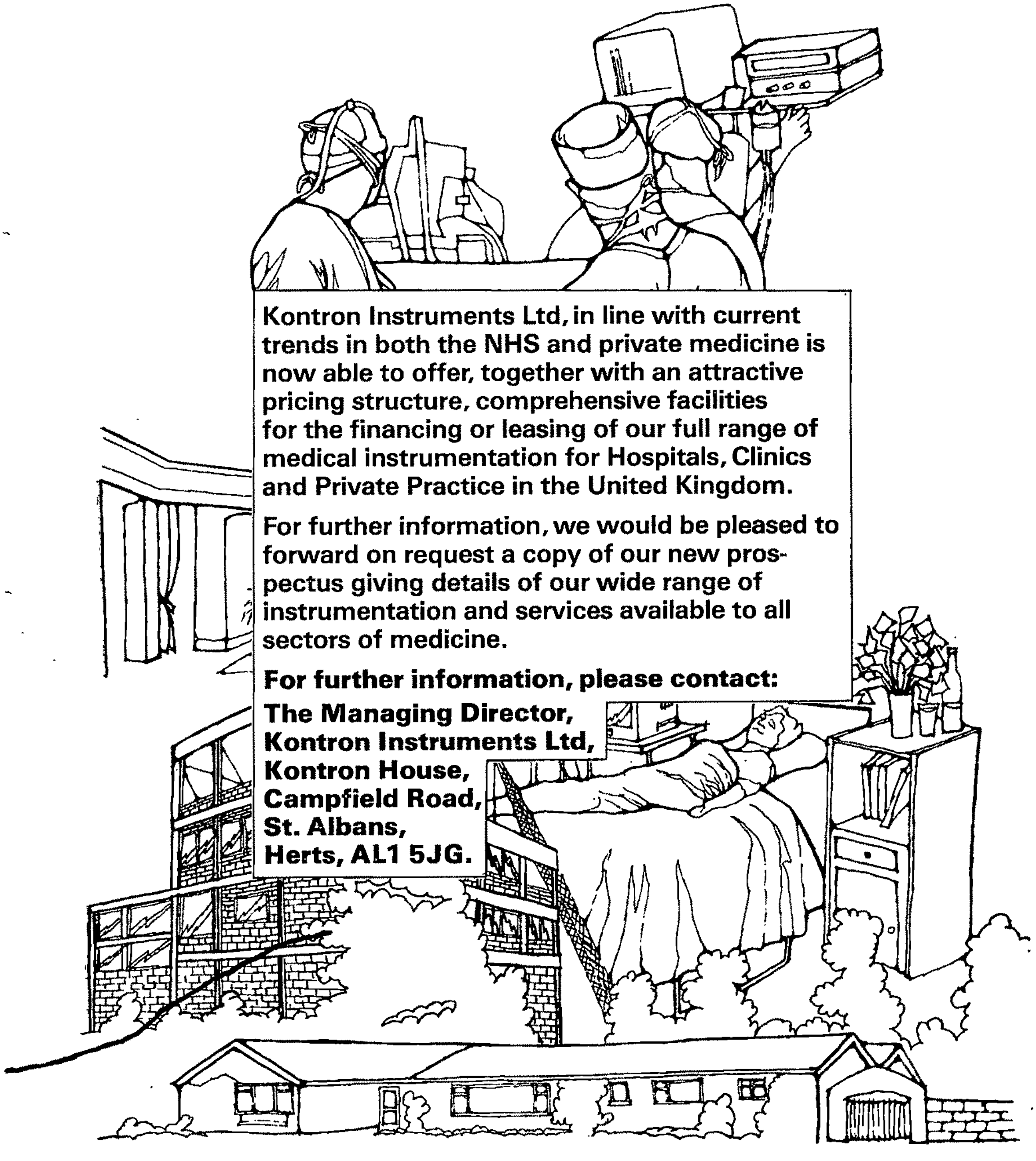

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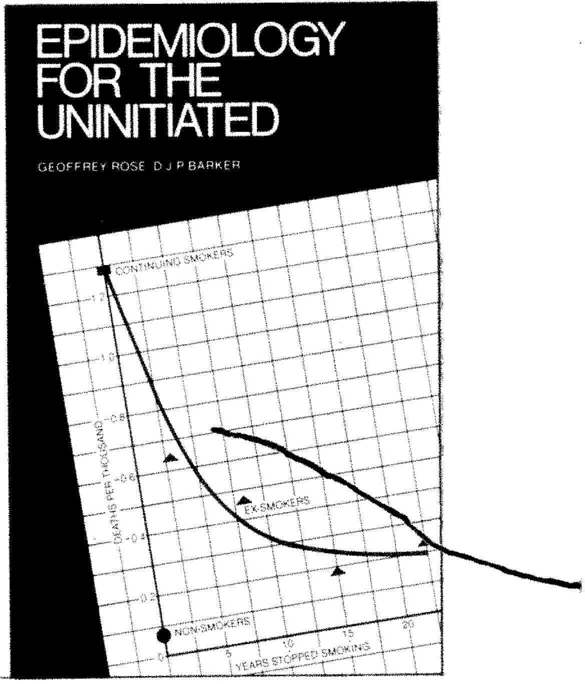

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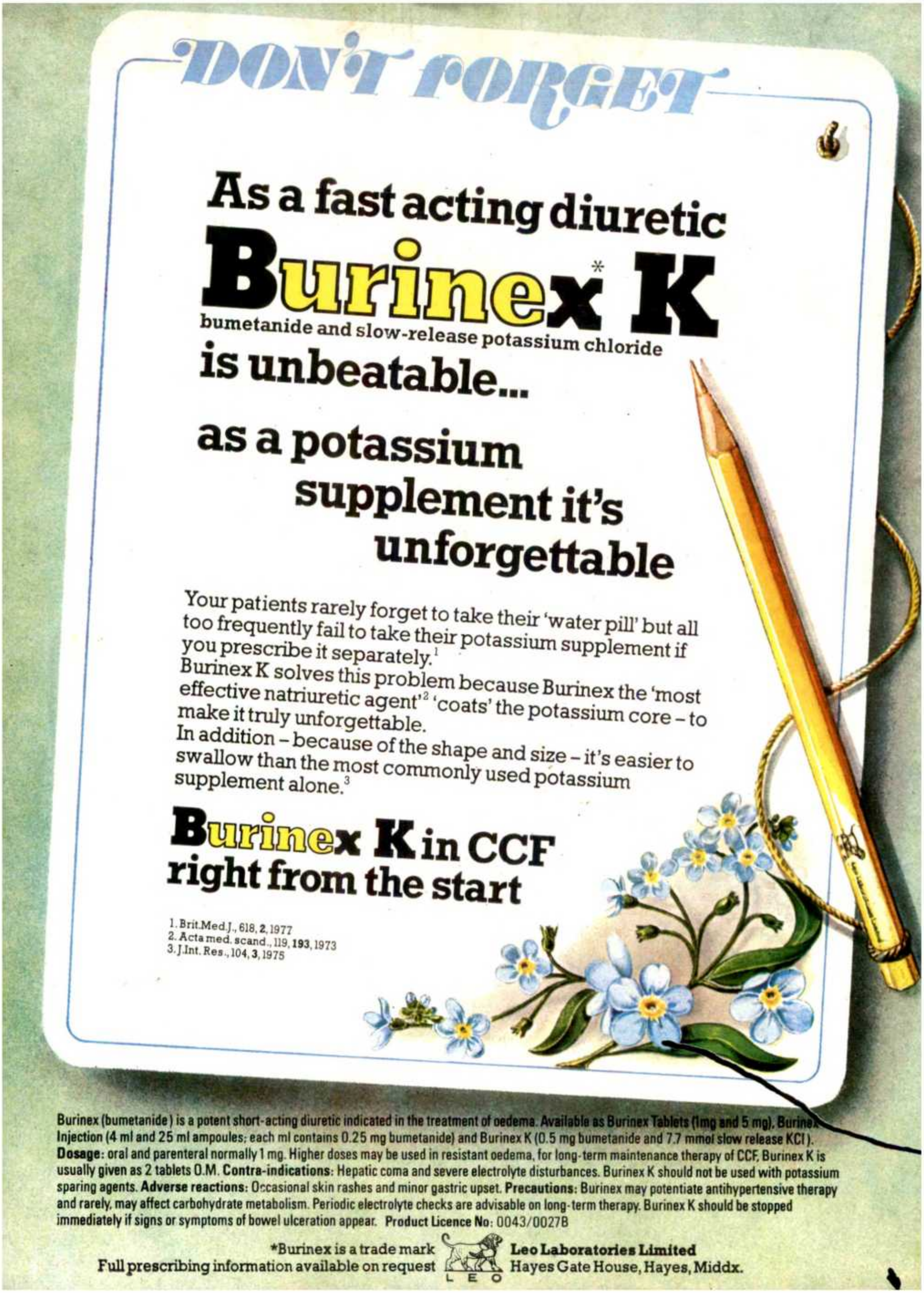

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British Heart Journal

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Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41:** 263–7.

(2) *Books and other monographs:*
Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977.* Edinburgh, London: Churchill Livingstone, 1978: 16–26.

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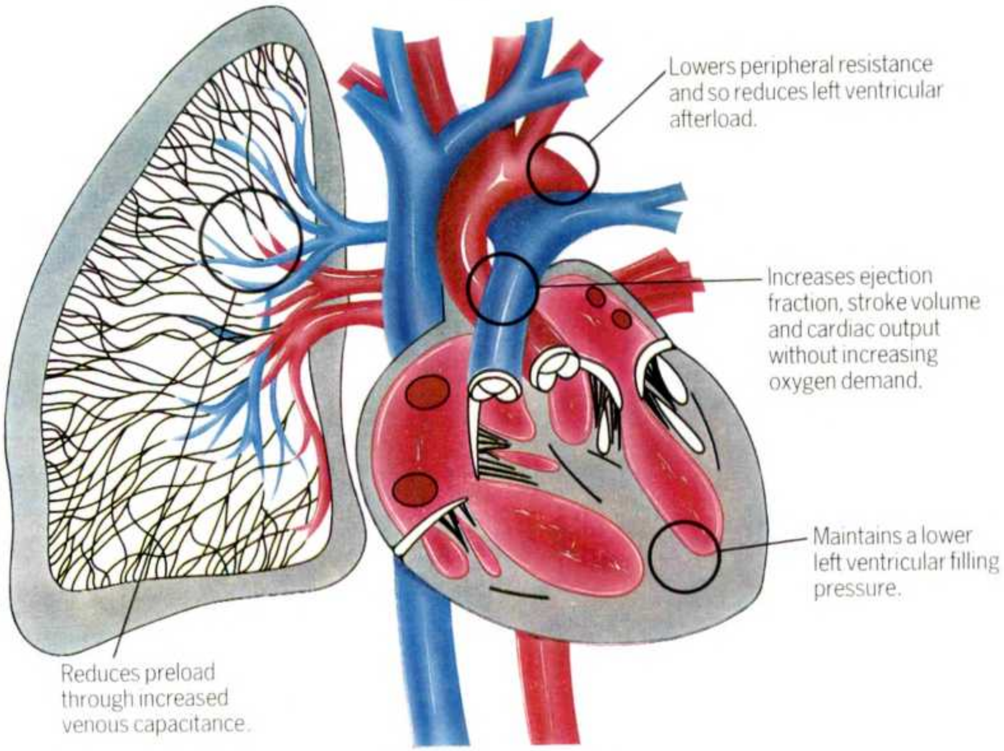
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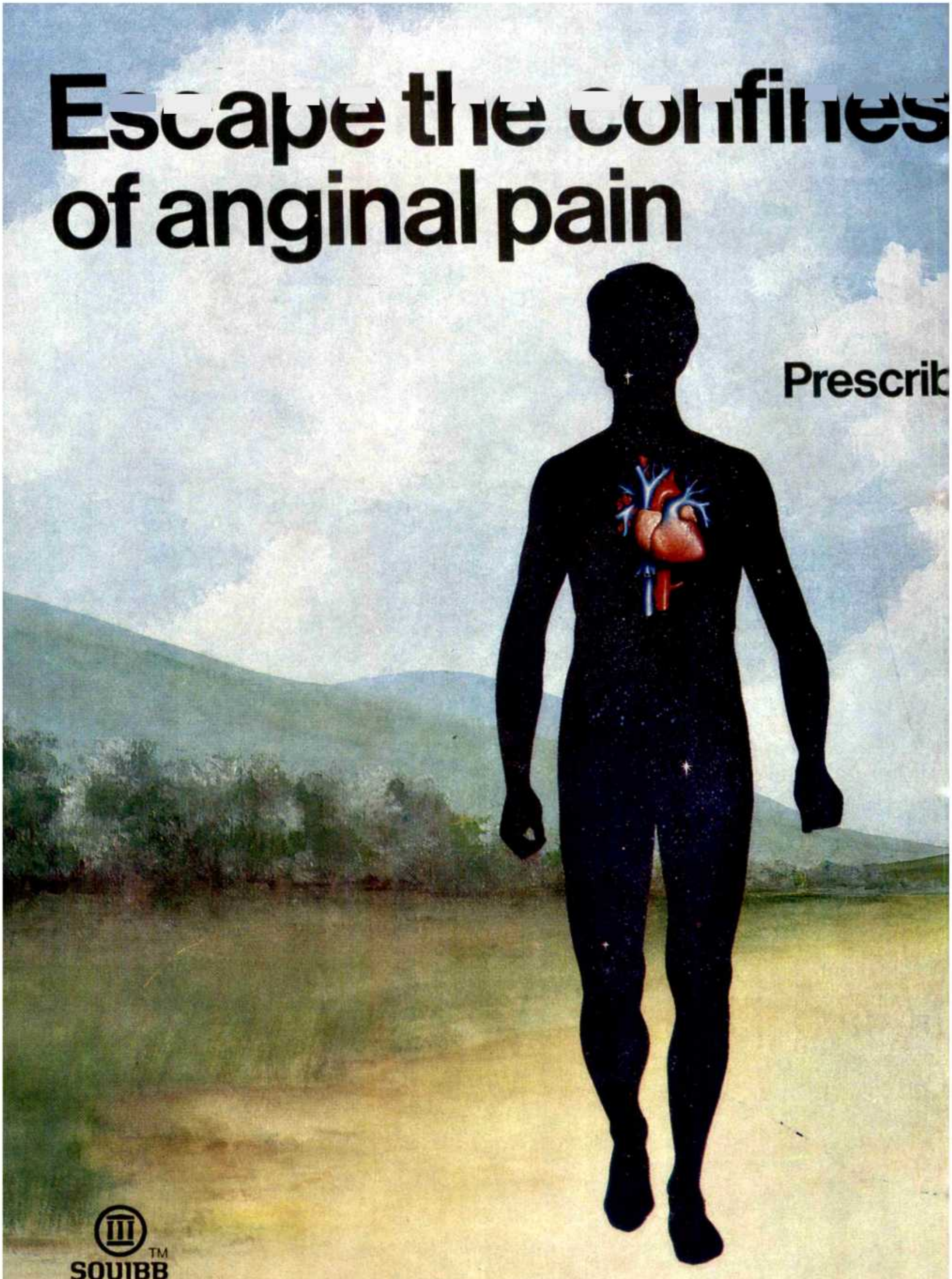

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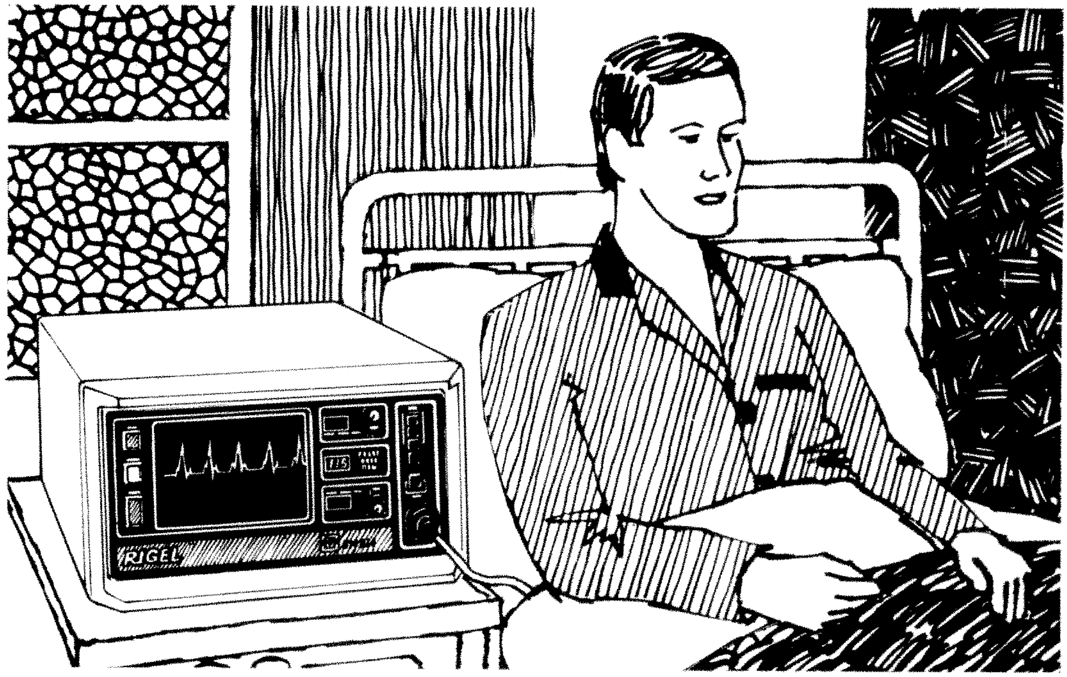

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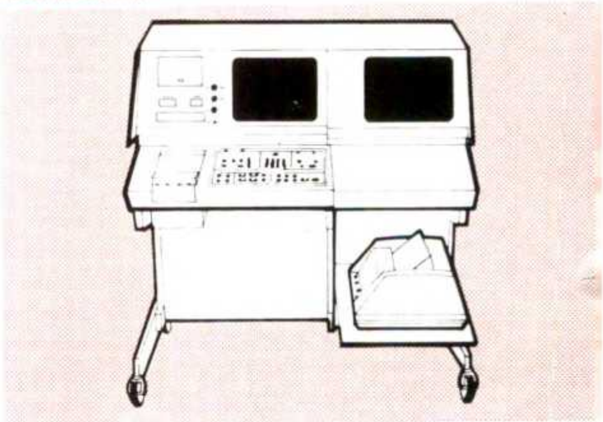

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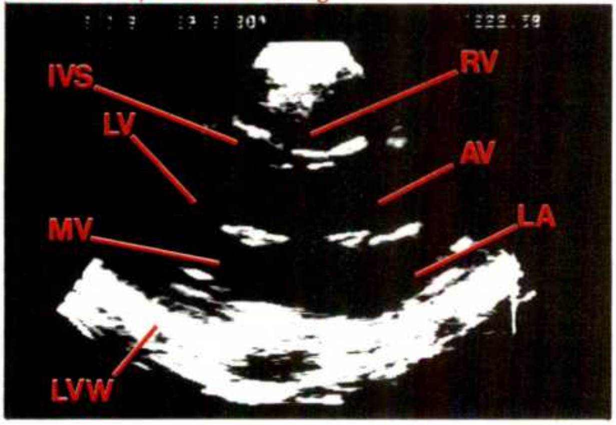

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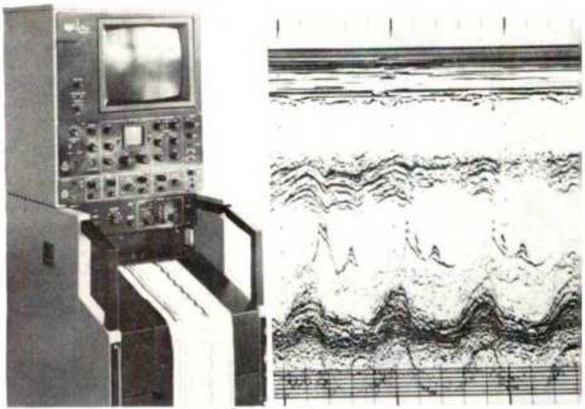

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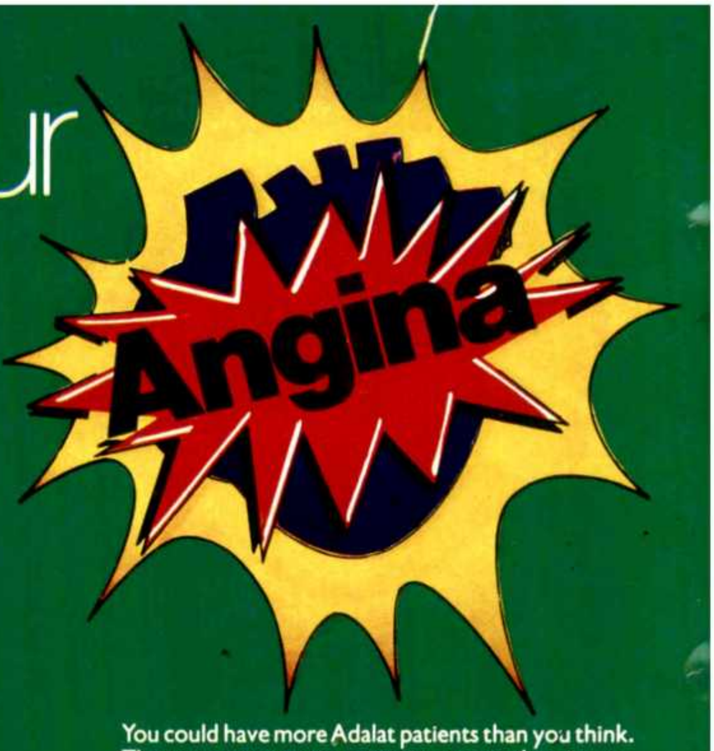

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Br Heart J 1980; **44:** 609–11

Correlations of fibrosis in endomyocardial biopsies from patients with aortic valve disease

P J OLDERSHAW, I A B BROOKSBY, M J DAVIES, D J COLTART,
B S JENKINS, M M WEBB-PEPLOE

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SUMMARY The amount of fibrosis in endomyocardial biopsies from 55 patients with aortic stenosis and 42 patients with aortic regurgitation was measured. Sixty per cent of the patients with aortic stenosis had some degree of fibrosis; the degree of fibrosis correlated strongly with ejection fraction, peak systolic gradient, symptoms of cardiac failure, and mortality. In patients with aortic regurgitation, fibrosis was found in 40 per cent and was never severe. A correlation was found with symptoms of cardiac failure and mortality at follow-up, but not with ejection fraction or degree of regurgitation.

Endomyocardial biopsy is used mainly to establish a pathological diagnosis in myocardial disease. Characteristic histological changes are seen in infiltrative disorders such as amyloidosis, sarcoidosis, and haemochromatosis but such cases are rare. In the majority of cases of acquired heart disease and of cardiomyopathy, microscopy of the diseased ventricle shows only non-specific changes such as fibrosis, increase in fibre size, vacuolation of muscle fibres, abnormal arrangement of muscle fibres, inflammatory cell infiltration, and alteration of cell organelles.[1 2] In this study, we set out to establish whether information obtained from the biopsy might predict patient prognosis.

The degree of fibrosis in endomyocardial biopsies from 97 patients with aortic valve disease was assessed. This was correlated with symptoms and the need for subsequent treatment of cardiac failure.

Methods

In this study, we included all patients who underwent cardiac catheterisation at St. Thomas' Hospital for aortic valve disease between 1973 and 1977. All gave informed consent for left ventricular biopsy. Each patient had right and left heart catheterisation including left ventricular angiography and coronary arteriography. Biopsies were taken with the modified Olympus fibreoptic bronchoscopic biopsy forceps[3] which was introduced using the St. Thomas' long sheath technique.[4] Specimens were taken from the left ventricle via the sheath passed either retrogradely across the aortic valve or transseptally across the mitral valve. Where possible, the sheath was positioned so that specimens were taken from the free wall of the left ventricle towards the apex. (Three or four specimens were taken from the ventricle in each case.) The specimens were fixed immediately in 10 per cent formol-saline solution, processed, and cut by conventional methods. Sections, 6 μ thick, were stained with haematoxylin and eosin and a modified trichrome, elastic van Gieson. The proportion of collagen was obtained in sections stained by the trichrome method, by means of a standard point-counting technique with a 25 point graticule in the eyepiece of the microscope. All specimens were analysed by a pathologist who was unaware of details of the patient's diagnosis.

The degree of fibrosis of the ventricle in each patient was compared with: (1) age of the patient; (2) the presence of hypertension before catheterisation (systolic blood pressure ≥140 mmHg), (3) electrocardiographic evidence of left ventricular hypertrophy (V1 S+V6 R≥35 mm); (4) coronary arteriographic evidence of ischaemic heart disease (stenosis ≥70% of normal vessel diameter); (5) ejection fraction as measured at cardiac catheterisation; (6) peak systolic gradient across the aortic valve or degree of aortic regurgitation; (7) the patient's symptoms and requirements for antifailure therapy.

All results are given as the mean ± the standard error of the mean. Differences between groups were assessed using Student's t test.

Received for publication 16 June 1980

Results

(a) PATIENTS

Left ventricular endomyocardial biopsies were obtained from 97 patients with aortic valve disease. In 55 of these patients (30 men, 25 women) aortic stenosis was the dominant lesion; in 42 (34 men, 8 women) aortic regurgitation was dominant. The mean age of patients with aortic stenosis was 59 years (range 30 to 72 years), and of those with aortic regurgitation 48 years (range 22 to 67 years). There was no correlation between degree of fibrosis and patient age or with duration of symptoms. Forty-two of the patients with aortic stenosis, and 25 of the patients with aortic regurgitation required aortic valve replacement.

Table 1 *Relation of percentage fibrosis to peak systolic gradient and ejection fraction (both measured at cardiac catheterisation) in patients with aortic stenosis*

Per cent fibrosis	*No. of patients*	*Mean peak systolic gradient (±SEM)*	*No. of patients with ejection fraction*		
			>0·55	*0·30–0·55*	*<0·30*
0	22	67 ± 9	15	7	—
0– 5	20	82 ±10	8	11	1
5–10	6	82 ±12	3	2	1
10–15	4	86 ±16	1	1	2
15–20	1	88	—	1	—
20–30	2	95	—	—	2

(b) AORTIC STENOSIS

Thirty-three (60%) of the 55 patients had fibrosis in the myocardial biopsy. The percentage fibrosis in these patients showed no significant correlation with pre-existing hypertension, electrocardiographic evidence of left ventricular hypertrophy, or coexisting ischaemic heart disease. There was, however, a significant correlation ($r=0{\cdot}78$, $p<0{\cdot}02$) with the left ventricular ejection fraction. The mean ejection fraction of patients with fibrosis was 0·43 as compared with 0·56 for patients without fibrosis ($p<0{\cdot}01$) (Table 1). Similarly, a significant correlation was found with the peak systolic gradient across the aortic valve as measured at cardiac catheterisation. Patients with fibrosis had a mean peak systolic gradient of 83 mmHg which was significantly greater than that for patients without fibrosis—67 mmHg ($p<0{\cdot}01$).

The percentage of fibrous tissue also correlated strongly with symptoms, the need for antifailure treatment, and mortality (Table 2). Of the 33 patients with fibrosis, 16 required antifailure therapy and 10 died during the follow-up period of this study; of the 22 patients without fibrosis only three required treatment and there were no deaths. Of the 10 patients with dominant stenosis who died, two died suddenly while waiting for surgery, two died during cardiac bypass, three died in the immediate postoperative period (one died with septicaemia, two died with presumed arrhythmia), and three died after discharge having had aortic valve surgery (one with increasing left ventricular failure, two undiagnosed).

Table 2 *Relation of percentage fibrosis to requirement for aortic valve replacement and medical antifailure treatment at follow-up in patients with aortic stenosis*

Per cent fibrosis	*No. of patients*	*No. of patients requiring aortic valve replacement*	*Follow-up treatment requirements*		
			No treatment	*Treatment*	*Dead*
0	22	15	19 (12)*	3 (3)	—
0– 5	20	16	6 (5)	10 (8)	4 (3)
5–10	6	5	1 (1)	2 (2)	3 (2)
10–15	4	3	—	3 (2)	1 (1)
15–20	1	1	—	1 (1)	—
20–30	2	2	—	—	2 (2)

*Numbers in parentheses indicate aortic valve replacement.

Twenty-seven (82%) of the 33 patients with fibrosis and 15 (68%) of the 22 patients without fibrosis had aortic valve replacement.

(c) AORTIC REGURGITATION

Fibrosis was found in 17 (40%) of the 42 patients; the percentage fibrosis, with the exception of one case, was less than 5 per cent. There was no correlation in these patients between percentage fibrosis and pre-existing hypertension, electrocardiographic evidence of left ventricular hypertrophy, or ischaemic heart disease nor with left ventricular ejection fraction or the degree of regurgitation. Percentage fibrosis was related to follow-up symptomatology and requirement for

Table 3 *Relation of percentage fibrosis to requirement for aortic valve replacement and to symptomatology at follow-up in patients with aortic regurgitation*

Per cent fibrosis	*No. of patients*	*No. of patients requiring aortic valve replacement*	*Follow-up treatment requirements*		
			No treatment	*Treatment*	*Dead*
0	25	15	22 (13)*	1 (1)	2 (1)
0– 5	16	9	10 (5)	4 (3)	2 (1)
5–10	—	—	—	—	—
10–15	1	1	—	1 (1)	—

*Numbers in parentheses indicate aortic valve replacement.

antifailure therapy (Table 3). In the absence of fibrosis, only one of 23 patients required antifailure treatment at follow-up, whereas five of 15 patients with fibrosis required such treatment. Of the 42 patients studied, four died in the follow-up period. Two of these had no fibrosis, two had less than 5 per cent fibrosis; two of these deaths followed cardiac arrests while the patients were awaiting aortic valve surgery, and two occurred several years after operation because of increasing left ventricular failure.

Ten (59%) of the 17 patients with fibrosis and 15 (62%) of the 24 patients without fibrosis had aortic valve replacement.

Discussion

To date, endomyocardial biopsy has been largely used to establish a pathological diagnosis and little work has been performed in trying to correlate histology with clinical findings. Two notable exceptions to this are found in the work of Kuhn *et al.*[5] and Kunkel *et al.*,[6] both of whom studied congestive cardiomyopathy. Kuhn *et al.*[5] concluded that endomyocardial biopsy allowed clear prognostic separation in patients with congestive cardiomyopathy, and was of diagnostic value in patients with mild cardiomegaly and a short history of symptoms. Kunkel *et al.*[6] also found good agreement in congestive cardiomyopathy between clinical and morphological changes. In this study, we have compared biopsy findings in patients with aortic valve disease with clinical symptomatology and mortality. Patients with aortic valve disease were used because their exercise tolerance remains poor after aortic valve replacement when left ventricular function is impaired preoperatively.[7] We measured the percentage of fibrosis in left ventricular biopsies from such patients to see if this was a contributory factor towards this effect.

In patients with dominant aortic stenosis, the degree of fibrosis showed good correlation with left ventricular function as assessed by the left ventricular ejection fraction at cardiac catheterisation, and also with the severity of the stenosis as measured by the peak systolic gradient across the aortic valve. The amount of fibrosis also proved useful in the prediction of prognosis, and correlated well with symptoms at follow-up, with requirements for antifailure therapy, and with mortality.

Patients with dominant aortic regurgitation developed fibrosis less frequently and to a less severe degree than patients with dominant stenosis. It was therefore difficult to relate fibrosis to left ventricular function or degree of regurgitation. The relation between percentage fibrosis and patient prognosis, however, still held.

In patients with either dominant aortic stenosis or regurgitation, there was no correlation with age, duration of symptoms, hypertension, electrocardiographic evidence of left ventricular hypertrophy, or coronary artery disease.

We suggest that the role of endomyocardial biopsy is not yet fully realised, and in the future this technique may be useful beyond simply establishing a pathological diagnosis.

References

1 Olsen EGJ. Diagnostic value of the endomyocardial bioptome. *Lancet* 1974; **i:** 658–60.

2 Brooksby IAB, Jenkins BS, Coltart DJ, Webb-Peploe MM, Davies MJ. Left ventricular endomyocardial biopsy. *Lancet* 1974; **ii:** 1222–5.

3 Richardson PJ. King's endomyocardial bioptome. *Lancet* 1974; **i:** 660–1.

4 Brooksby IAB, Swanton RH, Jenkins BS, Webb-Peploe MM. Long sheath technique for introduction of catheter tip manometer or endomyocardial bioptome into left or right heart. *Br Heart J* 1974; **36:** 908–12.

5 Kuhn H, Knieriem HJ, Lösse B, *et al.* Prognosis and possible presymptomatic manifestations of congestive cardiomyopathy (COCM). *Postgrad Med J* 1978; **54:** 451–9.

6 Kunkel B, Lapp H, Kober G, Kaltenbach M. Correlations between clinical and microscopic findings and natural history in congestive cardiomyopathy. In: Kaltenbach M, Loogen F, Olsen EGJ. eds. *Cardiomyopathy and myocardial biopsy*. Berlin: Springer, 1978; 271–83.

7 Brooksby IAB, Jenkins BS, Coltart DJ, Williams BT, Braimbridge MV, Webb-Peploe MM. Aortic valve replacement: the influence of ventricular function on the immediate and long term outcome. Eur Cong Cardiol.

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Br Heart J 1980; **44:** 612–20

Assessment of pulsed Doppler echocardiography in detection and quantification of aortic and mitral regurgitation*

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From the Section of Cardiology, Department of Medicine, Baylor College of Medicine and The Methodist Hospital, Houston, Texas, USA

SUMMARY Pulsed Doppler echocardiography was employed to detect disturbed or turbulent flow diagnostic of aortic or mitral regurgitation. Sensitivity, specificity, diagnostic accuracy, and predictive value were assessed by the independent interpretation and comparison of aortic root angiograms (91 patients) and left ventriculograms (94 patients) to the time interval histogram display of the pulsed Doppler. Sensitivity of Doppler in detecting mitral regurgitation was 94 per cent, with specificity 89 per cent, predictive value 81 per cent, and diagnostic accuracy 90 per cent (32 patients with, 62 without regurgitation). In aortic regurgitation, sensitivity was also 94 per cent, specificity 82 per cent, predictive value 94 per cent, and the diagnostic accuracy was 91 per cent (69 patients with, 22 without aortic regurgitation). Additionally, no Doppler evidence of mitral or aortic regurgitation was present in 20 normal subjects. The aetiology of left-sided valvular regurgitation varied widely, with prosthetic valvular insufficiency being the cause of mitral and aortic regurgitation in seven and 10 patients, respectively. Sixteen of 17 (94%) paraprosthetic leaks were correctly identified by pulsed Doppler. In patients with aortic regurgitation the flow-velocity curve recorded in the ascending aorta frequently showed a negative (or reversed) diastolic component, the magnitude of which (expressed as percentage negative area) correlated significantly with angiographic severity of regurgitation. Thus, pulsed Doppler echocardiography is a highly accurate and objective non-invasive technique for detecting mitral and aortic regurgitation. In aortic regurgitation, estimation of severity is possible from inspection of the Doppler ascending aortic flow velocity curve.

Pulsed Doppler echocardiography is a new non-invasive technique that has proved useful in the detection of valvular regurgitation or stenosis[1–3] as well as structural abnormalities such as atrial or ventricular septal defects.[4 5] The addition of pulsed Doppler studies to routine M-mode echocardiography enhances the likelihood of localising the source of cardiac murmurs and in certain instances quantifying the severity of valvular dysfunction. In this regard, we have recently shown[6] that analysis of the time interval histogram of the pulsed Doppler can be of use in discriminating between patients with severe aortic stenosis (aortic valve area less than 1·0 cm^2) and those with less severe stenosis (aortic valve area greater than 1·0 cm^2). Additionally, we have been able to quantify the amount of tricuspid regurgitation and relate the extent of regurgitation to right ventricular haemodynamics.[7]

Earlier reports concerning the diagnostic accuracy of pulsed Doppler echocardiography in detecting left-sided valvular regurgitation have depended primarily on a subjective interpretation of the audio output from the instrument to identify the presence of systolic turbulence in the left atrium, a sign of mitral regurgitation,[8] or diastolic turbulence in the left ventricular outflow tract, a sign of aortic regurgitation.[3] The obvious need for a graphic display of the data has led to the development of a time interval histogram for displaying the changes in frequency of the ultrasound.[9]

The objectives of this investigation were to

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determine the specificity, sensitivity, predictive values, and diagnostic accuracy of the time interval histogram in detecting the mitral and aortic regurgitation. Additionally, an attempt was made to correlate measurements derived from the time interval histogram with the angiographic severity of valvular insufficiency.

Materials and methods

TECHNICAL DESCRIPTIONS

The principles of pulsed Doppler echocardiography have been previously discussed by Johnson *et al.*[1] and Baker *et al.*[2] and will be reviewed only briefly. The frequency of a reflected sound wave is altered when the reflecting target is in motion. When an ultrasound beam is directed toward smooth, non-turbulent or laminar blood flow, the reflected sound waves exhibit a fairly uniform shift in frequency or "Doppler shift". This shift may be graphically represented as either a positive or negative deflection depending on direction of flow toward or away from the transducer. The magnitude of the shift is related to both velocity of flow and the angle of incidence between flow and sound. When the ultrasound beam is directed at turbulent blood flow, the reflected sound waves demonstrate a wide and random shift in frequency because of the varying direction and velocity of blood cells in the turbulent area.

Pulsed Doppler echocardiograms were performed in this study using a commercially available Echo-Doppler unit (advanced Technology Laboratory, Bellevue, Washington) that employs repetitive pulses of sound in the megaHertz range similar to traditional M-mode echocardiography. The advantage of pulsed Doppler over continuous wave Doppler is that the Doppler shifts produced by the velocity of blood flow can be recorded in localised intracardiac positions at variable depths by means of a range-gating system in conjunction with a standard M-mode echocardiogram, thereby allowing accurate placement of the sample volume within the cardiac chambers. An audio signal is generated, which is represented as tonal quality changes. Non-turbulent blood flow results in a narrow frequency band width producing a musical sound in contrast to turbulent flow which generates a wide band width pattern producing a harsh rasping sound.

In addition to the aural presentation, a permanent display of the Doppler shift is achieved using a time interval histogram. The time interval histogram plots the frequency shifts of the reflected ultrasound using a zero-crossing technique that has previously been described by Lorch *et al.*[9] In brief, a pattern is derived by measuring the time between successive zero crossings of audible signal wave forms. A zero crossing is defined as the instant in time when the Doppler shift signal

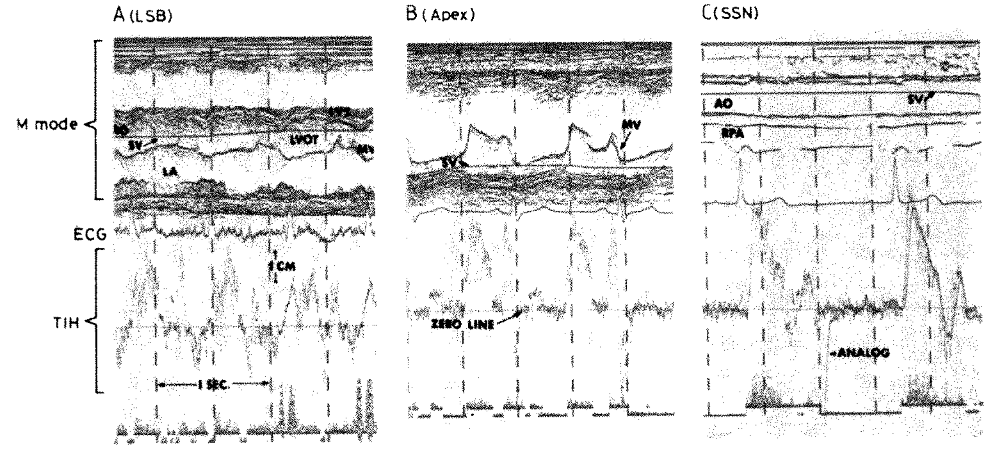

Fig. 1 *Examples of a normal pulsed Doppler echocardiographic examination with a compressed M-mode on top and a time interval histogram (TIH) below. The sample volume is placed in the left ventricular outflow tract (LVOT) when searching for aortic regurgitation (panel A) and posterior to the mitral valve (MV) when assessing mitral regurgitation (panel B). Panel C illustrates a normal ascending aortic flow velocity curve. The transducer location is shown in each panel in parentheses. LSB, left sternal border; SSN, supra-sternal notch; AO, ascending aorta; IVS, interventricular septum; LA, left atrium; RPA, right pulmonary artery; ECG, electrocardiogram.*

passes through its zero intensity level. A series of dots are printed above (positive shift) or below (negative shift) a baseline point. Each dot represents a zero crossing event with the distance away from baseline reflecting the magnitude of the Doppler shift frequency (the greater the frequency shift, the shorter the zero crossing time interval). Smooth laminar flow produces a narrow cluster of dots while disturbed or turbulent flow produces a widely dispersed dot pattern. The ultimate display consists of the M-mode echo with a superimposed line indicating the sample volume location, an electrocardiogram, and the time interval histogram (Fig. 1).

The technique employed in this study consisted of placing a 3·0 MHz transducer along the left sternal border in a fashion similar to a routine M-mode echocardiographic study (Fig. 1 and 2). The mitral and aortic valves as well as the left ventricular outflow tract and left atrium were identified with the M-mode echocardiogram. Threshold and gain settings were adjusted with the sample volume placed in the left atrium. Threshold was set at the lowest level that allowed a slight background noise on the baseline (any further reduction in threshold would produce wide dispersion of the dots giving an appearance of turbulent flow even though no real turbulence would be detected by the aural analysis). Gain was set at the highest level that allowed only a slight background noise to be audible.

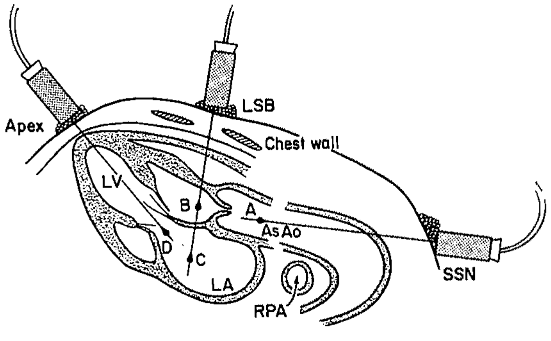

Fig. 2 *Diagrammatic illustration of the different transducer positions and sample volume locations (A-D) used in this study. See text for details. As AO, ascending aorta: other abreviations as in Fig. 1.*

Mitral regurgitation was sought from the left sternal border by placing the sample volume in the left atrium posterior to the anterior leaflet of the mitral valve or posterior to the aortic root while searching for systolic turbulence. In all cases the transducer was also placed at the cardiac apex with the patient in the left lateral recumbent position, the mitral valve was visualised, and the sample volume placed in the left atrium posterior to the anterior leaflet. When searching for turbulence, the operator relied on the audio output from the instrument while moving the sample volume around the left atrium making appropriate recordings when turbulence was heard. In all cases, however, the diagnosis of mitral regurgitation was ultimately based upon an objective analysis of the time interval histogram where turbulence was taken as a frequency dispersion greater than 10 mm (absolute measurement of dot distribution above and below the zero frequency shift baseline as shown in Fig. 3). When systolic turbulence was present, its maximal amplitude was measured in absolute millimetres from lines drawn outlining its upper and lower border (Fig. 3B). Measurements were averaged over the five cardiac cycles displaying widest frequency dispersion.

Aortic regurgitation was sought from the left sternal border by placing the sample volume in the left ventricular outflow tract (Fig. 4) just below the aortic valve, and searching for diastolic turbulence. As in mitral regurgitation, the diagnosis of aortic regurgitation was ultimately made from inspection of the time interval histogram. Special precaution in patients with left ventricular inflow obstruction (mitral stenosis or prosthetic mitral valves) was used to avoid confusion between diastolic turbulence produced by inflow through the mitral valve with that caused by aortic regurgitation. This potential source of error was prevented by sampling just below the aortic valve at a point where the M-mode echogram demonstrated the junction of the mitral valve anterior leaflet with the posterior aortic root echo. In all cases the transducer was also placed at the suprasternal notch with the sample volume in the ascending aorta for recording of the ascending aortic "flow-velocity" curve. Normally, the analogue of the time interval histogram in the ascending aorta produces a positive smooth "flow-like" curve during systole returning to baseline during diastole with only minimal early diastolic negative deflection (Fig. 1C). In aortic regurgitation without significant stenosis the diastolic curve frequently becomes negative consequent to retrograde flow into the ventricle (Fig. 4B). In these cases the areas of positive and negative deflections outlined by the analogue curve were measured by planimetry in five consecutive cardiac cycles and the results averaged to compute an index of severity of aortic regurgitation:

$$\%\ \text{negative area} = \frac{\text{negative area}}{\text{total area (negative plus positive areas)}} \times 100$$

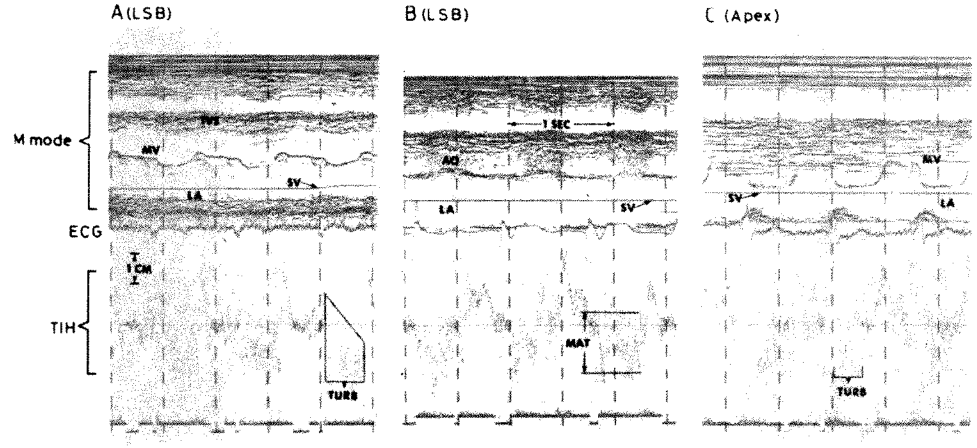

Fig. 3 *Examples of systolic turbulence (TURB) indicative of mitral regurgitation with sample volume located posterior to mitral valve (panels A and C) or in the left atrium (panel B); transducer position at left sternal border (panels A and B) or cardiac apex (panel C). The maximal amplitude of turbulence (MAT) is measured as shown in panel B. See text for details. Abbreviations as in Fig. 1.*

During a period of six months all patients who had a pulsed Doppler examination within five days of cardiac catheterisation were selected for analysis. The results from the Doppler time interval histogram were compared with the left ventricular or aortic root angiogram by independent observers. Left ventricular angiography was performed in all patients in a 30° right anterior oblique position with the injection of 40 to 50 ml Renografin-76 while the aortic root angiograms were performed in a 45° left anterior oblique projection with injection of similar amounts of contrast material. Mitral regurgitation was diagnosed from the left ventriculogram when contrast material appeared in the left atrium during systole in the absence of ventricular or atrial ectopy. The severity of mitral regurgitation was judged qualitatively as 1+ (rapid clearance of dye from the left atrium with each cycle), 2+ (slower clearance of dye from left atrium but greater opacification of ventricle than atrium), or

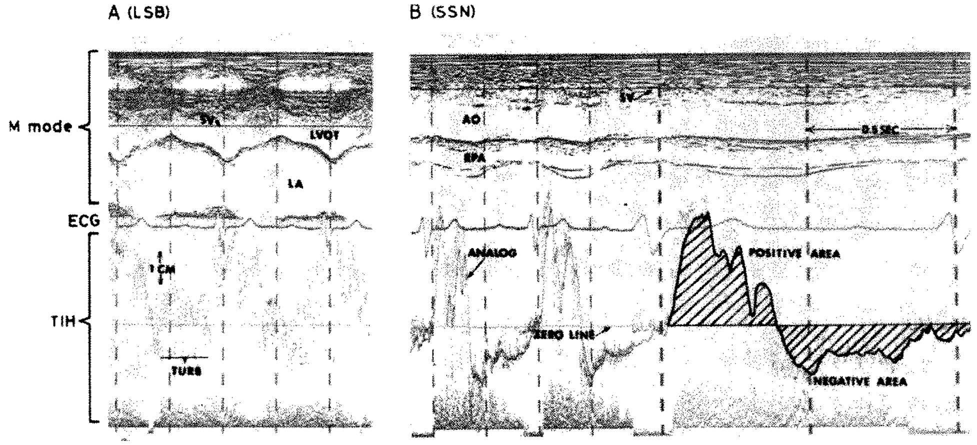

Fig. 4 *Panel A shows an example of diastolic turbulence (TURB) in the left ventricular outflow tract indicative of aortic regurgitation; transducer positioned at left sternal border. Panel B illustrates an ascending aortic flow velocity curve from the same patient showing a characteristic diastolic negative deflection. Planimetry of the negative and positive areas allows assessment of severity of aortic regurgitation (see text). Abbreviations as in Fig. 1.*

3+ (left atrium filled with dye and appearing equal to or more dense than ventricle). Aortic regurgitation was diagnosed from the aortic root angiogram when contrast material appeared in the left ventricle during diastole; its severity was judged qualitatively from 1+ to 4+: 1+, minimal dye in the ventricle clearing with each systole; 2+, slower clearance of dye from ventricle with aortic opacification greater than ventricular; 3+, rapid opacification of ventricle with slow clearance and equal density of dye in both ventricle and aorta; 4+, complete opacification of ventricle within first two cardiac cycles with greater density of dye in the ventricle than in the aorta.

Four patients were eliminated from analysis, two for suboptimal echocardiographic studies and two for suboptimal quality of the angiograms. The decision to eliminate these patients was made without knowledge of the results of the angiogram in the first two or the Doppler examination in the second two cases. A total of 94 studies was available for comparison with angiographic detection of mitral regurgitation and 91 for comparison with angiographic detection of aortic regurgitation. In addition, 20 normal subjects without evidence of organic heart disease were studied by pulsed Doppler echocardiography to establish specificity for mitral and aortic regurgitation in a normal population. The sensitivity, specificity, predictive value, and accuracy of the pulsed Doppler echocardiogram were calculated as follows:

$$\text{Sensitivity} = \frac{\text{true positive}}{\text{true positive plus false negatives}}$$

$$\text{Specificity} = \frac{\text{true negative}}{\text{true negative plus false positives}}$$

$$\text{Predictive value} = \frac{\text{true positive (or negative)}}{\text{true positive (or negative) plus false positive (or negative)}}$$

$$\text{Accuracy} = \frac{\text{true positives plus true negatives}}{\text{all subjects}}$$

where, true positive = Doppler positive, angio positive; true negative = Doppler negative, angio negative; false negative = Doppler negative, angio positive; and false positive = Doppler positive, angio negative. The significance of a difference between the means of samples was computed using Student's t test with significance established at a $p < 0{\cdot}05$ level.

Results

MITRAL REGURGITATION

Fig. 3 shows examples of mitral regurgitation detected from either left sternal border or apical approaches. Fig. 5 illustrates the sensitivity, specificity, and predictive values of Doppler in detecting mitral regurgitation. Angiographic evidence of mitral regurgitation was present in 32 out of 94 patients. Table 1 lists the aetiologies of mitral regurgitation in these patients. The pulsed Doppler time interval histogram detected mitral regurgitation in 30 of the 32 patients (94% sensitivity). Mitral regurgitation was absent by Doppler in 55 out of 62 patients without angiographic evidence of

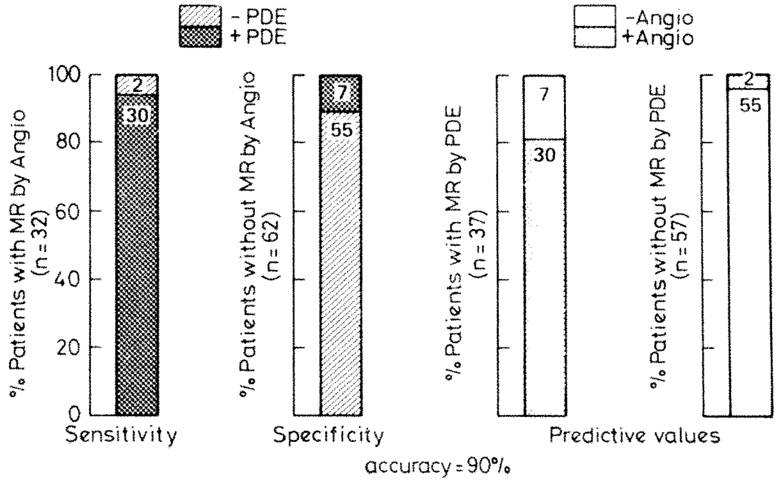

Fig. 5 *Bar diagram illustrating sensitivity, specificity, and predictive values of pulsed Doppler echocardiography (PDE) in mitral regurgitation (MR). Angio, angiography.*

regurgitation (89% specificity). The predictive values for a positive and a negative Doppler examination were 85 per cent and 96 per cent, respectively, while the overall diagnostic accuracy was 90 per cent. Both false negative examinations occurred in patients with minimal (1+) angiographic mitral regurgitation. The seven false positive Doppler studies consisted of four patients with cardiomyopathy, and one each with aortic stenosis and left ventricular failure, mitral valve prolapse, and ventricular septal defect. None of the 20 normal subjects had evidence of mitral regurgitation by Doppler.

Table 1 *Aetiology of mitral regurgitation in 32 patients*

Aetiology	*Angio MR*	*PDE MR*
Rheumatic	13	12
Prosthetic valve leak	7	6
Myxomatous valve	5	5
Cardiomyopathy	3	3
Papillary muscle dysfunction	3	3
Congenital defect	1	1
Total	32	30

Angio, angiographic; MR, mitral regurgitation; PDE, pulsed Doppler echocardiography.

Mitral regurgitation was detected from a single location in 19 patients and from multiple locations in 11 patients. In patients having regurgitation noted from a single location, turbulence was detected only in the left atrium in two, behind the mitral valve with the transducer at the left sternal border in eight, and behind the mitral valve with the transducer placed at the apex in nine. Turbulence was located in early systole in 10 patients, mid or late systole in six, and was holosystolic in 14. No correlation ($p > 0{\cdot}05$) was observed between duration or location of turbulence and angiographic severity of mitral regurgitation.

The maximum amplitude of systolic turbulence was 15·9 ± 1·0 mm (mean ± standard error), 18·9 ± 1·9 mm, and 21·8 ± 1·4 mm in patients with 1+, 2+, and 3+ mitral regurgitation, respectively. While a tendency for greater amplitude of turbulence to occur with increasing severity of mitral regurgitation was suggested, the overlap between individual values was such that only the comparison of 1+ versus 3+ (15·9 versus 21·8 mm) achieved statistical significance at the 0·05 level.

AORTIC REGURGITATION

Fig. 4A illustrates an example of aortic regurgitation detected with the sample volume in the left ventricular outflow tract. Fig. 6 illustrates the sensitivity, specificity, and predictive values of pulsed Doppler in detecting aortic regurgitation. Angiographic evidence of aortic regurgitation was present in 69 out of 91 patients; the time interval histogram of the pulsed Doppler was positive in 65 out of 69 patients (94% sensitivity). Aortic regurgitation was absent by Doppler in 18 out of 22 patients without angiographic evidence of aortic regurgitation (82% specificity). The predictive value for a positive and negative Doppler examination was 94 per cent and 82 per cent, respectively; the overall diagnostic accuracy was 91 per cent. The different aetiologies of aortic regurgitation are listed in Table 2.

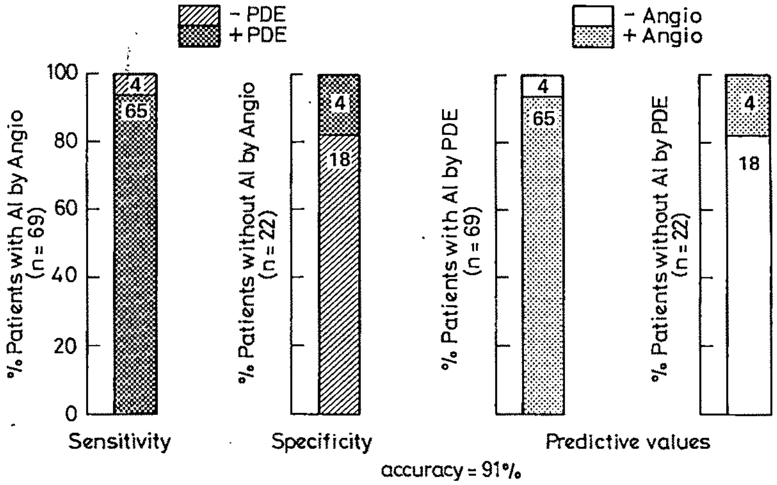

Fig. 6 *Bar diagram illustrating sensitivity, specificity, and predictive values of pulsed Doppler echocardiography (PDE) in aortic insufficiency (AI). Angio, angiography.*

The four false negative Doppler examinations occurred in patients with minimal (1+) angiographic aortic regurgitation. The four false positive Doppler studies consisted of three patients with rheumatic heart disease and evidence of aortic valve thickening by M-mode echocardiography, and one patient with a membranous ventricular septal defect, severe pulmonary hypertension, and significant right-to-left shunting. None of the 20 normal subjects had evidence of aortic regurgitation by Doppler.

Neither the duration nor the amplitude of diastolic turbulence in the left ventricular outflow tract correlated with the angiographic severity of aortic regurgitation. In contrast, the analogue of the time interval histogram "flow-velocity" curve recorded in the ascending aorta with the transducer in the suprasternal notch frequently demonstrated a negative diastolic component (Fig. 4B). The magnitude of negative deflection, measured as the percentage negative area in 54 of the 69 patients with aortic regurgitation, was found to relate significantly ($p<0{\cdot}05$) with the qualitative angiographic assessment of severity of regurgitation. As shown in Fig. 7, the percentage negative area was $8{\cdot}9 \pm 2{\cdot}9$ (mean ± SEM) for patients with 1+, $23{\cdot}6 \pm 4{\cdot}2$ for 2+, $35{\cdot}7 \pm 5$ for 3+, and $50{\cdot}2 \pm 6{\cdot}5$ for 4+ aortic regurgitation. A 30 per cent or less negative area was noted in 26 out of 31 (84%) patients with 2+ or less aortic regurgitation, while a negative area greater than 30 per cent was present in 17 out of 23 (74%) patients with 3+ or more regurgitation. Thus, using a less or greater than 30 per cent negative deflection to discriminate between mild ($\leqslant$2+) and severe ($\geqslant$3+) aortic regurgitation, the predictive value of the pulsed Doppler was 81 and 77 per cent, respectively, with a diagnostic accuracy of 80 per cent.

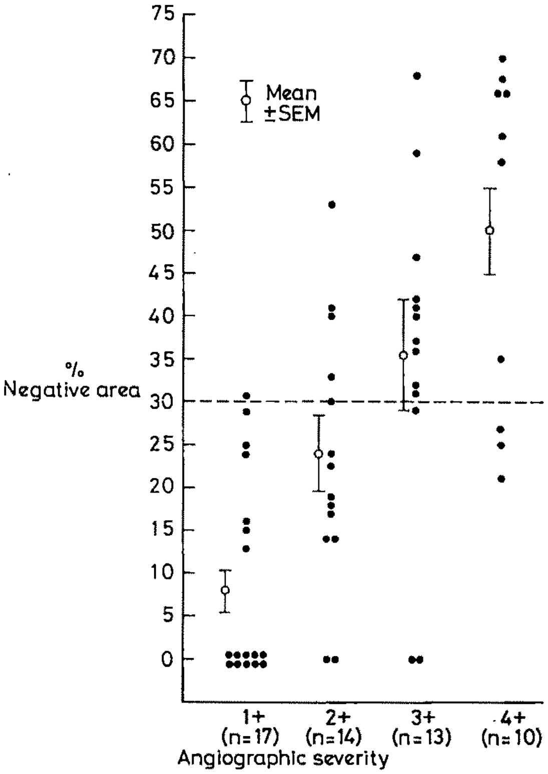

Fig. 7 *Scatter diagram illustrating the percentage negative area of the ascending aortic flow velocity curve in patients with aortic regurgitation when compared with angiographic severity.*

Discussion

Pulsed Doppler echocardiography allows assessment of intracardiac and aortic flow-velocity patterns not provided by standard M-mode echocardiography. The recent development of a graphic display of the frequency shifts of the reflected sound waves has made it possible to record and evaluate objectively flow-velocity patterns, even though an accurate measurement of flow velocity is still not possible with the commercially available system. Despite this limitation, the results of this investigation demonstrate a high (90% and 91%) accuracy for this technique in detecting both mitral and aortic valvular regurgitation when angiography was used as the standard for comparison. The sensitivity for detection of either lesion was 94 per cent with all of the false negative cases having minimal regurgitation at angiography. The specificity for mitral regurgitation was 89 per cent, with six of the seven false positive patients having either left ventricular dilatation with failure (five patients) or mitral valve prolapse (one patient), conditions in which mitral regurgitation may be present inconsistently.

Table 2 *Aetiology of aortic regurgitation in 69 patients*

Aetiology	*Angio AR*	*PDE AR*
Rheumatic	36	32
Calcific	12	12
Prosthetic valve leak	10	10
Dilated aortic root	6	6
Endocarditis	2	2
Congenital defect	2	2
Myxomatous valve	1	1
Total	69	65

AR, aortic regurgitation; others as in Table 1.

The specificity for aortic regurgitation was 82 per cent. Three of the four false positive cases had significant aortic valve thickening by echocardiography, with varying degrees of stenosis observed during cardiac catheterisation. The fourth false positive case of aortic regurgitation had a membranous ventricular septal defect with pulmonary hypertension and a significant right-to-left shunt; presumably the diastolic turbulence detected in the left ventricular outflow tract originated from diastolic right-to-left shunting through the septal defect since the diastolic filling pressures in the right ventricle exceeded that in the left (35 versus 8 mmHg). None of the 20 normal subjects tested had Doppler evidence of mitral regurgitation or aortic regurgitation. If these subjects are considered as true negatives, the specificity of the technique for mitral and aortic regurgitation becomes 91 and 90 per cent, with an accuracy of 92 and 93 per cent, respectively. These results are comparable to previous reports on detection of mitral and aortic regurgitation by pulsed Doppler echocardiography.[3 8] The previous investigations, however, were solely dependent on the subjective interpretation of the audio output from the instrument by the technician performing the study while the present study relied on an objective interpretation of the time interval histogram.

Although the diagnosis of mitral or aortic regurgitation in this investigation was made from an objective inspection of the time interval histogram, the technical skills of the operator remain an important factor in obtaining an optimal study. Detection of mitral regurgitation is a clear example of this. Mitral regurgitation was detected from a single location in 19 out of 30 patients, the left sternal border approach being no more sensitive than the apex (eight of 19 versus nine of 19); in the remaining 11 patients mitral regurgitation was detected from multiple locations. Thus, accurate recognition of left-sided valvular regurgitation at the time of the procedure requires use of a standardised search procedure with placement of the sample volume visually guided by the compressed M-mode and aurally directed by the valve and flow sounds indigenous to the various chambers. In addition, appropriate recordings must be supervised carefully by the technicians performing the study to ensure accurate reproduction of the aural findings.

A potential limitation of the pulsed Doppler technique may occur when clinical situations demand examination with the sample volume located a long distance from the transducer. This problem may be manifest when mitral regurgitation is sought from the cardiac apex. As Fig. 2 indicates, the sample volume is near the distal limits of the range-gate when placed in the left atrium or immediately posterior to the mitral valve with the transducer at the apex. At these deeper sites within the heart, the pulse repetition frequency (range 3500 to 10 000 pulses per second) must be diminished to avoid ambiguous echoes, the net result being an increase in the minimum Doppler shift that can be detected. Theoretically, this might decrease the sensitivity for detection of mitral regurgitation since milder cases may not create sufficiently large Doppler shifts to be recognised. Despite this potential limitation, the sensitivity of pulsed Doppler for mitral regurgitation in this study was 94 per cent and, interestingly, this lesion was detected solely through the apical approach in nine patients.

The aetiological causes of mitral and aortic regurgitation in the present study were multiple and included the entire spectrum of valvular heart disease seen in adult cardiology. Both structural lesions (such as rheumatic, myxomatous, and calcific disease) as well as functional disturbances (such as left ventricular dilatation with papillary muscle dysfunction or ascending aortic aneurysms with loss of aortic valve support) were frequently observed. The accuracy of pulsed Doppler in detecting regurgitation was similar in each of these entities. Importantly, 17 patients had prosthetic valves with paravalvular leaks, including seven mitral and 10 aortic prosthetic valves. Of these 17 patients, 16 or 94 per cent were accurately detected by pulsed Doppler when compared with angiography; the one false negative consisted of a patient with a mitral prosthesis and minimal regurgitation. Accurate assessment of patients with valvular prostheses represents an important contribution of pulsed Doppler echocardiography to the clinical evaluation of these patients since paraprosthetic leaks are frequently difficult to confirm by either physical examination or by standard M-mode echocardiography.

Optimal determination of the severity of valvular regurgitation by Doppler analysis requires quantification of regurgitant flow. The present instrumentation, however, does not afford precise measurement of flow or velocity of flow. Nevertheless, if the angle between sound and blood flow remains constant, changes in the area under the "flow-velocity" curve should reflect changes in flow. Using this basic assumption, a comparison was made between the degree of reverse, or negative, diastolic flow in the ascending aorta (expressed as per cent negative area) and a qualitative angiographic assessment of the severity of aortic regurgitation. Using 30 per cent negative area as the separation point, this simple measurement yielded an 81 per cent and 77 per cent predictive value for differentiating mild ($\leqslant 2+$) versus severe ($\geqslant 3+$) aortic regurgitation, respectively (Fig. 6). Angiographic measurements of regurgitant fractions were not made in these patients. It is conceivable that such a precise assessment of degree of regurgitation might even relate to the percentage negative area by Doppler better than the qualitative assessment.

Determination of severity of aortic regurgitation echocardiographically has relied primarily on evaluating the degree of the left ventricular dilatation and the "volume overload" pattern of wall motion, both of which are haemodynamic consequences rather than a true measurement of regurgitation; both are also dependent upon obtaining a high quality echocardiographic view of the left ventricle. Our experience has been that a pulsed Doppler ascending aorta flow-velocity curve can be recorded easily in the vast majority of patients regardless of the difficulty in obtaining an adequate image by standard M-mode techniques. The results presented herein suggest that analysis of this curve provides a direct index of aortic regurgitation.

A rough correlation was observed in the present study between the qualitative angiographic assessment of severity of mitral regurgitation and the achieved maximal amplitude of turbulence detected be Doppler. Statistical significance ($p < 0{\cdot}05$), however, was achieved only for the comparison between 1+ and 3+ mitral regurgitation, and thus the application of this Doppler measurement to individual patients with mitral regurgitation is very limited.

Future improvements in the instrumentation and signal processing of the data will further enhance the ability of this new non-invasive technique to detect and quantify valvular regurgitation. The results of this investigation, however, indicate that in its present state, pulsed Doppler echocardiography has become a useful clinical adjunct to the non-invasive evaluation of patients suspected of having left-sided valvular regurgitation.

References

1 Johnson SL, Baker DW, Lute RA, Dodge HT. Doppler echocardiography; the localisation of cardiac murmurs. *Circulation* 1973; **48:** 810–22.

2 Baker DW, Rubenstein SA, Lorch GS. Pulsed Doppler echocardiography: principles and applications. *Am J Med* 1977; **63:** 69–80.

3 Ward JM, Baker DW, Rubenstein SA, Johnson SL. Detection of aortic insufficiency by pulse Doppler echocardiography. *JCU* 1977; **5:** 5–10.

4 Goldberg SJ, Areias JC, Spitaels SEC, de Villeneuve VH. Use of time interval histographic output from echo-Doppler to detect left-to-right atrial shunts. *Circulation* 1978; **58:** 147–52.

5 Stevenson JG, Kawabori I, Dooley T, Guntheroth WG. Diagnosis of ventricular septal defect by pulsed Doppler echocardiography: sensitivity, specificity and limitations. *Circulation* 1978; **58:** 322–6.

6 Young JB, Quinones MA, Waggoner AD, Miller RR. Diagnosis and quantification of aortic stenosis by pulsed Doppler echocardiography (abstract). *Circulation* 1978; **58,** suppl II: 42.

7 Waggoner AD, Quinones MA, Verani MS, Miller RR. Pulsed Doppler echocardiographic detection of tricuspid insufficiency: diagnostic sensitivity and correlation with right ventricular hemodynamics (abstract). *Circulation* 1978; **58,** suppl II: 41.

8 Johnson SL, Baker DW, Lute RA, Murrary JA. Detection of mitral regurgitation by Doppler echocardiography (abstract). *Am J Cardiol* 1974; **33:** 146.

9 Lorch G, Rubenstein S, Baker D, Dooley T, Dodge H. Doppler echocardiography: use of a graphical display system. *Circulation* 1977; **56:** 576–85.

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Primary myxomatous degeneration of cardiac valves

*Clinical, pathological, haemodynamic, and echocardiographic profile**

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SUMMARY Four hundred and ninety-nine surgically excised valves were examined for pathological evidence of myxomatous degeneration. Thirty-six valves (7%) had myxomatous degeneration as a major pathological finding. Fourteen valves (3%) had significant myxomatous degeneration of the *pars fibrosa*, a finding which we define as "primary myxomatous degeneration". Echocardiographic findings and catheterisation results were correlated with the clinical course, surgical results, and follow-up in these 14 patients. Echocardiograms in 10 of the 11 patients who had them (91%) showed abnormalities suggesting the presence of primary myxomatous degeneration. Echocardiography was more helpful than angiography in diagnosis. The histological pattern of primary mitral myxomatous degeneration appears to be identical to that seen in patients with mitral valve prolapse and five of six patients with mitral lesions had echocardiographic evidence of prolapse. None of the patients with primary myxomatous degeneration of the aortic valve had syphilis or Marfan's syndrome. While the aetiology of primary myxomatous degeneration of cardiac valves is not known, a link to a more generalised disorder is suggested.

Myxomatous degeneration of cardiac valves has aroused considerable interest.[1–13] Evidence has accumulated to suggest that this is the predominant pathology in patients with mitral valve prolapse.[14–19] Myxomatous degeneration has been found in patients with isolated mitral regurgitation,[3 4 6] aortic regurgitation,[1] and combined mitral and aortic regurgitant lesions.[1 2]

Much confusion surrounds the concept of myxomatous degeneration of cardiac valves. Some investigators maintain that it is the result of one specific disease process.[4] Others characterise it as a non-specific tissue response to a variety of factors.[1] Myxomatous degeneration has been considered a normal ageing change, an associated finding in congenital heart disease,[1] a response to syphilitic aortitis, and the result of rheumatic heart disease.[1 12 20]

Depending on the criteria used to define the entity and the population studied, the percentage of subjects with myxomatous degeneration of cardiac valves varies widely. If one accepts the view that this is the pathology causing mitral valve prolapse,[14 16–19] as many as 6 per cent of healthy adults and 9 to 16 per cent of patients undergoing valve replacement in the United States may have it.[1 2 5 12]

The clinical significance of myxomatous degeneration has been widely debated. Mitral valve prolapse has been linked to an increased incidence of arrhythmias,[21–24] a higher risk of subacute bacterial endocarditis,[25] and a greater chance of sudden death.[26 27] Patients whose regurgitant lesions are the result of myxomatous degeneration have been retrospectively found to have endocardial friction lesions,[28] ruptured chordae tendineae,[2 15 28] a higher incidence of bacterial endocarditis,[2] and an increased risk of intraoperative complications.[2 3] The current study was undertaken to examine the clinical consequences of this pathological process.

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Subjects and methods

(a) PATIENTS

Pathological data were reviewed from all patients who underwent replacement of one or more cardiac valves at the Peter Bent Brigham Hospital between 1 January 1974 and 1 June 1977. Of the 499 patients in this category, 36 had myxomatous degeneration of their cardiac valves as a major pathological finding (8%).

(b) PATHOLOGY

Histological sections and macroscopic appearances of the cardiac valves from these 36 patients were reviewed in detail by one of us (MCF) who had no knowledge of the clinical findings. In this study, primary myxomatous degeneration was defined as degeneration of collagen of the *pars fibrosa* of the valve with basophilic staining in this region caused by the deposition of acid mucopolysaccharides (proven by special histochemical techniques), in the absence of severe calcification or fibrosis, and no macroscopic evidence of rheumatic valvular disease (shortening, fusion, and thickening of the chordae tendineae of atrioventricular valves or commissural fusion of semilunar valves) (Fig. 1).

It is important to emphasise that the key pathological feature, the entity which we define as *primary* myxomatous degeneration, involves significant disruption of the *pars fibrosa*. While the amount of myxomatous material found in the *pars spongiosa* was also increased in our patients, this latter feature is a common pathological finding and may represent a non-specific response to ageing,[12] or to a diverse number of underlying pathological conditions ranging from rheumatic valvular disease to Marfan's syndrome.[10]

Fourteen patients were found to have primary myxomatous valvular degeneration by the criteria outlined above. Seven of these had undergone mitral valve replacement, six aortic valve replacement, and one replacement of both mitral and aortic valves. Of the remaining 22 patients with myxomatous degeneration of their cardiac valves as a prominent finding, but without *primary* myxomatous degeneration, 11 had degeneration secondary to rheumatic heart disease, three had "presumed" papillary muscle dysfunction, two showed congenital malformations, one had calcific aortic stenosis, one had infective endocarditis, one had syphilitic aortitis, one had plasmacytic aortitis, and two were of uncertain cause.

(c) ECHOCARDIOGRAPHY

Echocardiograms were available on 11 of the 14 patients with primary myxomatous degeneration. These studies were recorded on Irex or Smith-Kilne ultrasound equipment interfaced with Irex strip chart recorders and 2·25 megaHertz transducers. Echocardiograms were obtained using standard techniques, with the mitral valve, tricuspid valve and aortic root imaged in the usual fashion.[29] Echocardiograms in these patients with severe mitral regurgitation were examined independently by three experienced echocardiographers who were unaware of both clinical information regarding the patients and the echocardiographic interpretations of their colleagues.

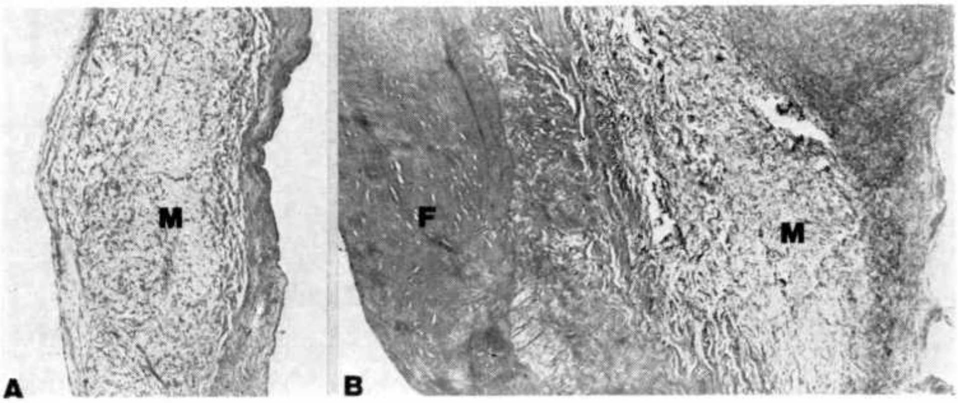

Fig. 1 *(A) Primary myxomatous degeneration. The valve is thin with a distinct increase in myxomatous (M) tissue (H. and E. ×48). (B) Secondary myxomatous degeneration from a patient with rheumatic mitral valvular disease. There is pronounced thickening of the valve leaflet caused mainly by an increase in fibrous (F) tissue. There is only a focal area of myxomatous (M) degeneration (H. and E. ×48).*

(d) CATHETERISATION

Cardiac catheterisation had been performed in 12 patients. Angiograms were available for nine patients, with both a left ventricular angiogram and an aortogram in six cases, a left ventricular angiogram alone in two cases, and an aortogram alone in one case. Haemodynamic data were analysed in these patients, and a scoring system was designed to characterise haemodynamic status as a function of left ventricular end-diastolic pressure, cardiac index, and estimated left ventricular wall motion. Ejection fraction could not be calculated in most instances because left ventricular images were too large to fit in their entirety on a cineangiogram frame. Mitral and aortic regurgitation were graded from the left ventricular angiograms and aortograms in nine patients and from written reports in three patients. Grading was from 0 to 4+ using standard angiographic criteria.[30]

To study the angiographic presence of mitral valve prolapse in five patients with mitral regurgitation in whom angiograms were available, the end-systolic left ventricular angiographic frame from the right anterior oblique projection was traced onto paper, with special attention paid to the outline of the mitral valve. These tracings, together with similar tracings of nine normal subjects, were graded as to the degree of mitral valve prolapse by three experienced angiographers in ignorance of the clinical data. Tracings were used instead of the actual angiograms to eliminate possible bias introduced by the presence of mitral regurgitation.

Results

CLINICAL DATA

Clinical data for the 14 patients are summarised in Table 1. The sex incidence was equal.Ages ranged from 29 to 73 years. All had had congestive cardiac failure for periods ranging from six months to six years. Ten of the 14 patients had experienced either a sudden onset or a distinct exacerbation of symptoms within the 10 months before surgery. All patients had significant murmurs of mitral and/or aortic regurgitation. Systolic clicks, confirmed by phonocardiography, were noted in three instances. No patient had a Marfan habitus, ectopia lentis, or arachnodactyly. There was one probable case of infective endocarditis, though no organisms could be cultured from this patient's valve.

ECHOCARDIOGRAPHIC DATA

Echocardiographic data are summarised in Table 2. Echocardiograms were performed in six of the seven patients with mitral regurgitation, four of the six patients with aortic regurgitation, and in the patient with disease of both valves. Left ventricular volume overload patterns compatible with mitral regurgitation were noted in all six patients with the mitral valve lesion. Late systolic prolapse of the mitral valve, or bulging of the entire mitral valve apparatus toward the left atrium throughout systole was seen in five of these. Five, too (83%) also showed echoes diagnostic of ruptured chordae tendineae.[31] Two of the six, reported elsewhere,[32] had dilatation of the

Table 1 *Clinical data: primary myxomatous degeneration*

		Historical data				*Physical examination*			*Laboratory data*	*Follow-up*
Case no.	*Sex*	*Age (y)*	*Congestive heart failure*	*Chest pain*	*Palpitation*	*Subacute bacterial endocarditis*	*Clicks*	*Murmurs*	*Electrocardiogram*	
Mitral valve disease										
1	F	64	+	+	—	—	—	MR	1° AV block	Doing well 30 mth postop
2	M	62	+	—	+	—	+	MR	AF, AMI	Died 48 h postop
3	M	46	+	—	+	—	—	MR	LVH, RVH	Doing well 35 mth postop
4	F	70	+	+	+	—	+	MR	1° AV block	Doing well 36 mth postop
5	M	52	+	+	+	—	—	MR	AF, LVH	Doing well 30 mth postop
6	M	55	+	+	—	—	—	MR, AR	A fl, LVH, RVH	Died 24 h postop
7	M	57	+	+	—	—	—	MR	AF, LVH	Doing well 26 mth postop
Aortic valve disease										
8	F	29	+	—	—	+	—	SEM, AR	LAE, LVH	Doing well 36 mth postop
9	F	73	+	—	—	—	—	AR, MR	Non-specific ST and T wave changes	Died 72 h postop
10	F	59	+	+	—	—	—	SEM, AR	LVH	Doing well 26 mth postop
11	M	35	+	—	—	—	—	SEM, AR	LVH	Doing well 36 mth postop
12	F	65	+	—	—	—	—	SEM, AR	LVH	Doing well 34 mth postop
13	F	55	+	+	+	—	+	SEM, AR	LVH	Doing well 24 mth postop
Aortic and mitral valve disease										
14	M	50	+	—	—	—	—	AR, MR	LAE, LVH	Doing well 36 mth postop

Abbreviations: AF, atrial fibrillation; AMI, anterior myocardial infarction; AR, aortic regurgitation; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; MR, mitral regurgitation; A fl, atrial flutter; RVH, right ventricular hypertrophy; SEM, systolic ejection murmur.

aortic root and tricuspid valve prolapse in addition to mitral valve prolapse (Fig. 2). Three of the four patients with aortic valve myxomatous degeneration who had echocardiograms showed significant dilatation of the aortic root. In these three the aortic valve itself appeared normal though excursion was small in relation to the aortic root (Fig. 3). Additional abnormal aortic echoes were present in two of these patients, possibly representing leaflet redundance, but though mitral valve prolapse was not documented in any of them, tricuspid valve prolapse was seen in one patient. Echocardiography in the patient with disease of both valves showed only left ventricular volume overload and mitral valve fluttering secondary to aortic regurgitation.

Table 2 *Echocardiographic data: primary myxomatous degeneration*

Case no.	*Aortic root (cm/m^2) [nl < 2·2 cm]*	*Aortic valve excursion (cm)*	*Left atrium (cm/m^2) [nl < 2·1 cm/m^2]*	*Right ventricular diameter (cm/m^2) [nl < 1·1 cm/m^2]*	*Mitral valve excursion (mm) [nl=20–35 mm]*	*Interventricular septum thickness (mm) [nl=9–11 mm]*	*Left ventricular post wall thickness (mm) [nl=9–11 mm]*	*Left ventricule D_d (cm)^2*	*Left ventricule D_s (cm)^3*	*Tricuspid valve excursion*
Mitral valve disease										
1	2·1		3·1		25	13	13	4·7	2·2	
2	1·8	1·9	3·6	2·2	35	10	12	6·8	4·6	Prolapse
4	1·8	1·7	4·0		38	9	10	7·0	4·8	Normal
5	1·9	2·0	3·7	1·3	28	9	9	7·1	6·0	Normal
6	2·3	1·8	3·2	0·9	30	10	11	8·5	5·9	Normal
7	2·1	2·3	2·9	1·5	33	12	11	5·9	3·0	Prolapse
Aortic valve disease										
8	1·9	2·1	2·2	0·9	12	9	11	5·5	3·4	Normal
11	2·5		2·6	6·0	24	10	12	8·2	6·2	Normal
12	2·5	1·3	2·0	7·0	12	12	11	6·8	4·2	Normal
13	2·7	1·6	2·4	1·0	22	10	8	6·5	4·5	Normal
Aortic and mitral valve disease										
14			3·6				10	6·8	3·9	

Abbreviations: D_d, diastolic diameter, D_s, systolic diameter.
Note: No echocardiogram was done in cases 3, 9, and 10.

CATHETERISATION DATA

Cardiac catheterisation was performed in six of the seven patients with primary myxomatous degeneration of the mitral valve and in five of the six patients with degeneration of the aortic valve. Significant angiographic valvular regurgitation was shown in all of these patients. Left ventricular function varied considerably, with no discernible pattern; in two patients it was good, in five modestly depressed, and in four severely compromised. Angiograms from five of the six patients with mitral valve disease were available for study of mitral valve prolapse by our three observers using tracings of the valve. Prolapse was judged to be present in only five of 15 possible observations (33%), but in no instance was there unanimous agreement among the observers about individual tracings (Fig. 4). In the five patients with aortic valve disease who had angiograms, dilated aortic root was shown in one patient, a dilated ascending aorta in another, and a type III dissecting aneurysm in a third.

SURGICAL RESULTS

Surgical findings and complications are summarised in Table 3. Mitral valve replacement was performed in all seven patients with mitral valve disease. Ruptured chordae tendineae were confirmed in five instances, and a dilated mitral valve annulus was found in five patients. A "floppy" appearance of the mitral valve was noted in three patients.

In four of the six patients with aortic valve disease, valve replacement alone was performed, while in two patients repair of an aortic aneurysm was also carried out. Several types of macroscopic valvular pathology were noted. Three patients had thin aortic leaflets and one patient had evidence of cusp destruction consistent with infective endocarditis.

Serious operative complications occurred in three patients: two experienced hypotension unresponsive to pressors and balloon counterpulsation (both dying within 48 hours of surgery), a third suffered a cerebrovascular accident of the right hemisphere, and haemostasis could not be achieved in a fourth who died 72 hours after operation.

PATHOLOGICAL FINDINGS

All excised valves fulfilled the criteria for primary myxomatous degeneration described above. On macroscopic examination, no valve showed commissural fusion. One mitral valve had focal chordal fusion, but the diffuse chordal abnormalities chacteristic of rheumatic valvular disease[33] were not present. Superimposed infective endocarditis was seen in one aortic valve. On microscopical examination, all valves showed prominent and uniform myxomatous degeneration of the *pars fibrosa* (Fig. 1). Some degree of fibrosis without calcification was present in all valves.

FOLLOW-UP

Patients surviving operation have done well postoperatively (see Table 1). Follow-up periods have ranged from 24 to 36 months (mean=31·7) with all patients free from major complications or symptoms of congestive cardiac failure.

Comments
Typical ruptured chordae tendineae
Typical ruptured chordae tendineae; dilated aortic root; mitral valve prolapse throughout systole; tricuspid valve prolapse
Typical ruptured chordae tendineae; mitral valve prolapse
Mitral valve prolapse throughout systole; left ventricular dysfunction (PEP/ET=0·87)
Typical ruptured chordae tendineae; mitral valve prolapse throughout systole
Typical ruptured chordae tendineae; aortic root dilatation; mitral valve prolapse; tricuspid valve prolapse
Diastolic aortic valve gap; tricuspid valve prolapse
Aortic root enlarged
Aortic root enlarged
Aortic root enlarged
Mitral valve flutter secondary to aortic regurgitation

Discussion

PATHOLOGY OF MYXOMATOUS DEGENERATION

Considerable confusion surrounds the concept of myxomatous degeneration of cardiac valves and its relation to various disease states, in part arising from failure adequately to define myxomatous degeneration. General agreement exists on the histological pattern described by Sherman *et al.*[6] that "Myxomatous transformation is pathologically characterised by disruption and loss of normal valvular architecture accompanied by an increase in ground substance with no appreciable inflammatory reaction". Biochemical studies have shown that the abnormally increased ground substance in myxomatous degeneration is an acid mucopolysaccharide.[7 34]

Numerous conditions including ageing,[10] rheumatic heart disease,[1] and Marfan's syndrome,[35] have been associated with some degree of valvular myxomatous degeneration. As reported in the present study, primary myxomatous degeneration can be distinguished from these entities by histological criteria. The reported histological findings in the few valves excised from patients with mitral valve prolapse[14 18 19] appear to be identical to those of our patients with primary myxomatous degeneration.

Early investigations of myxomatous degeneration of the aortic valve linked this pathological entity to more generalised connective tissue disorders and suggested that it might be an arrested form of Marfan's syndrome.[4] Several subsequent studies failed to corroborate this[1 2] and none of our patients had features of Marfan's syndrome. The condition is said to be commoner in men, but five of our six patients were women.

The other underlying conditions in secondary as well as in primary myxomatous degeneration which are possible causes of myxomatous degeneration were not found in our study.[10] Our data support the observations of Pomerance[10] and Roberts and Virmani[33] that primary myxomatous degeneration can be distinguished from that secondary to rheumatic heart disease. No patient had positive serology for syphilis, and none had congenital abnormalities. The average age of our patients was relatively low (55 years). Nevertheless, while no specific underlying aetiology was found, the presence of tricuspid and aortic valve prolapse in addition to mitral valve prolapse in two of our patients (14%) and the presence of aortic aneurysms or aortic annular dilatation in three patients (21%) raise the possibility of a more generalised disorder.

INCIDENCE AND CLINICAL RELEVANCE OF PRIMARY MYXOMATOUS DEGENERATION

Previous studies have offered very different estimates of the incidence of myxomatous degeneration of cardiac valves.[1 2 30] These differences may be in part the result of the problems of definition already mentioned. A small degree of myxomatous degeneration is probably present in most cardiac valves, and may represent a non-specific change on ageing[20] or a response to normal haemodynamic stress.[12] If the criteria outlined above for the diagnosis of primary myxomatous degeneration are insisted upon, the incidence appears quite low—in our study 3 per cent (14/499).

The relation between primary myxomatous degeneration and mitral valve prolapse remains a significant and largely unanswered question. Interestingly, five of our six patients with primary myxomatous degeneration of the mitral valve had preoperative echocardiographic evidence of mitral valve prolapse. Whether the converse is always true is uncertain.

It has been argued that patients with primary valvular myxomatous degeneration show rapid clinical deterioration once symptoms appear, have more complications at operation, and do less well after it than patients who have valvular regurgitation of other kinds.[2 3] Preoperative catheterisation studies in our patients showed a wide range of ventricular function and symptoms that had been present for anything from months to years. The rapidity of clinical deterioration is difficult to assess, since many of our patients were referrals from other institutions, but it is our impression that this was no greater in general than expected. Most of our patients with mitral regurgitation had experienced

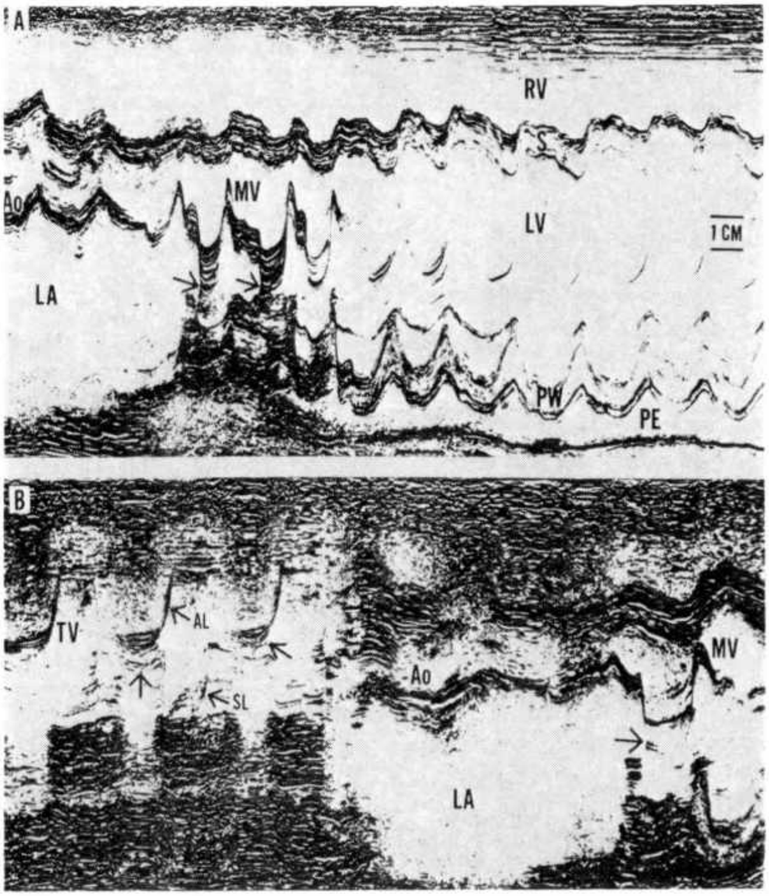

Fig. 2 *Patient with primary myxomatous degeneration of the mitral valve, mitral and tricuspid valve prolapse, and dilatation of the aortic root (case 2). (A) Echocardiographic "sweep" of the left ventricle from the base toward the apex. The mitral valve (MV) shows pronounced systolic prolapse (unlabelled arrows) and hypermobility of the prolapsing valve components. The left atrium (LA) is much enlarged as is the left ventricle (LV) and right ventricle (RV). There is a pericardial effusion (PE) seen posteriorly. PW, posterior wall; S, septum; Ao, aortic root. (B) Echocardiographic sweep (continuous recording) from the tricuspid valve (TV) through the aortic root (Ao) to the mitral valve (MV). There is an increased excursion of the anterior (AL) and septal leaflets (SL) as well as systolic prolapse of both anterior and septal leaflets. A hypermobile portion of the mitral valve (unlabelled arrow) is also seen prolapsing back towards the left atrium (LA) as in (A).*

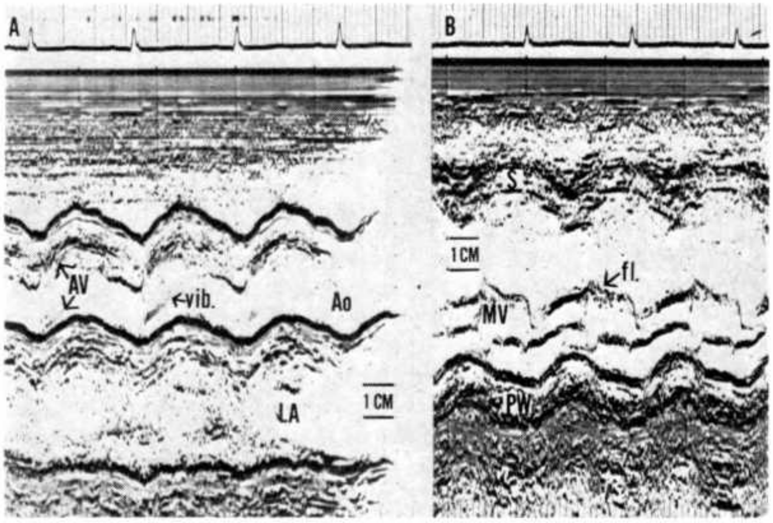

Fig. 3 *Patient with primary myxomatous degeneration of the aortic valve. (A) Echocardiogram of the aortic root (Ao), aortic valve (AV), and left atrium (LA). There is prominent high frequency vibration (vib) of the aortic leaflets. (B) Echocardiogram of the mitral valve and base of the left ventricle. The mitral valve (MV) shows diastolic fluttering (fl.) of aortic regurgitation. PW, posterior wall; S, septum.*

an acute onset of symptoms, a finding consistent with the high incidence of ruptured chordae tendineae in them.

Complications at operation are difficult to assess. In one of our 14 patients (7%) bleeding was hard to control, a non-specific finding. There were no instances of dissection at clamp sites or of valvular dehiscence, problems previously reported in patients with primary valvular myxomatous degeneration.[2] Prognosis remains in question. At first glance, the perioperative mortality rate of 21 per cent (three deaths in 14 patients) in our patients appears alarmingly high, particularly as the current mortality rate for valvular replacement at our hospital is less than 5 per cent, but two of the patients who died had severely compromised ventricular function before operation and the third patient had a dissecting aortic anaeurysm. Follow-up in the 11 remaining patients for periods ranging from 24 to 36 months suggests a generally favourable course.

PREDICTIVE VALUE OF ECHOCARDIOGRAPHY AND ANGIOGRAPHY IN PRIMARY MYXOMATOUS DEGENERATION

In previous studies of primary myxomatous

Table 3 *Surgical data: severe myxomatous degeneration*

Case no.	*Procedure*	*Operative findings*	*Complications*
Mitral valve disease			
1	MVR 31 mm porcine	RCT ant. leaflet MV	R hemisphere CVA
2	MVR 35 mm porcine	RCT; "floppy" MV; dilated MV annulus; pericardial adhesions	Hypotension, ? bleeding; died 48 hours postop
3	MVR 33 mm porcine	"Floppy" MV; RCT anterior leaflet MV	None
4	MVR large ball valve	"Floppy" MV; 3 RCT post leaflet MV; dilated MV annulus	Hypotension responsive to pressors
5	MVR 35 mm porcine	Very dilated MV annulus	None
6	MVR 35 mm porcine	RCT; massively dilated MV annulus	Hypotension; died 24 hours postop
Aortic valve disease			
8	AVR	Severe destruction of AV caused by SBE	None
9	AVR; replace ascending aorta	"Floppy" AV; aneurysm of ascending and descending aorta	Intraoperative oozing; died 72 hours postop; LV rupture
10	AVR 23 mm porcine	"Floppy" AV	None
11	AVR 27 mm porcine	AV leaflets heavily rolled with central orifice	None
12	AVR 23 mm porcine; replace ascending aorta	Aneurysm of ascending aorta; stretched aortic annulus	None
13	AVR 21 Björk-Shiley	"Floppy" AV	None
14	AVR	"Floppy" AV; dilated ascending aorta	None
Aortic and mitral valve disease			
15	AVR 27 mm porcine MVR 33 mm porcine	"Floppy" AV and MV	None

Abbreviations: AV, aortic valve; AVR, aortic valve replacement; CVA, cerebrovascular accident; MV, mitral valve; MVR, mitral valve replacement; RCT, ruptured chordae tendineae, SBE, subacute bacterial endocarditis.

degeneration, no echocardiographic data have been reported.

Eleven of our patients had echocardiograms and in 10 of them the diagnosis of primary myxomatous degeneration was suggested by this examination. Echocardiograms were particularly helpful in degeneration of the mitral valve where prolapse and/or a pattern suggesting ruptured chordae tendineae were shown in all patients. In patients with degeneration of the aortic valve, dilatation of the aortic root was a common, helpful finding.

In contrast, catheterisation data were less helpful. While regurgitant lesions were shown in all 13 patients, no specific haemodynamic or angiographic pattern emerged for patients with mitral regurgitation, though three of those with aortic regurgitation had an aneurysm or root dilatation.

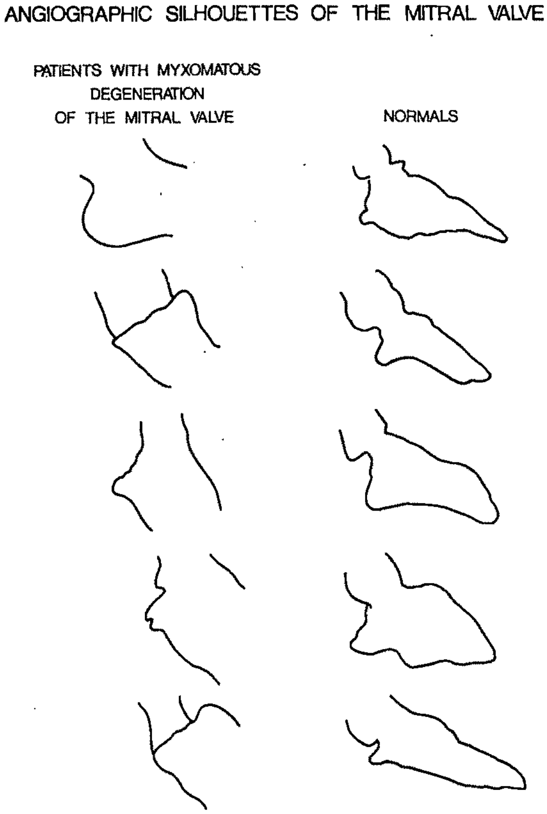
ANGIOGRAPHIC SILHOUETTES OF THE MITRAL VALVE
PATIENTS WITH MYXOMATOUS DEGENERATION OF THE MITRAL VALVE
NORMALS

Fig. 4 *Angiographic silhouettes of the mitral valve. Tracings were taken from the end-systolic left ventricular angiographic frame in the RAO projection. Tracings from the five patients with myxomatous degeneration of the mitral valve who had cardiac catheterisation are on the left. Tracings of five normal controls used for comparison are on the right.*

For years, the relative merits of echocardiography versus angiography in documenting mitral valve prolapse have been debated.[36–40] In our patients, all with pathologically proven primary myxomatous degeneration, a pure form of the pathology thought to underly mitral valve prolapse, echocardiography was diagnostic in 83 per cent of cases, with 100 per cent observer agreement, but angiography, in contrast, showed mitral valve prolapse in only 33 per cent of frames studied and observer agreement was not unanimous.

Conclusion

Using the criteria defined in this study, primary myxomatous degeneration was an infrequent pathological finding in 499 valves replaced for aortic or mitral regurgitation, occurring in approximately 3 per cent. It can usually be distinguished pathologically from rheumatic and other forms of valvular disease. Its aetiology is unknown. Previous suggestions that it may be secondary to syphilitic aortitis, congenital heart disease, or Marfan's syndrome were not confirmed, but the presence of other cardiac abnormalities in a high percentage of the patients suggests that it may be part of some more generalised disorder. The pathological findings of primary myxomatous degeneration are indentical to those seen in patients with clinical mitral valve prolapse. Valve replacement may carry a higher than normal mortality (21% of our patients died) though the small number of patients and the presence of other clinical complications make this uncertain. Nevertheless, the possibility, which previous reports have also suggested underlines the importance of making the diagnosis preoperatively. Echocardiography appears to be more useful than angiography in diagnosis.

References

1 Frable WJ. Mucinous degeneration of the cardiac valves—the "floppy valve" syndrome. *J Thorac Cardiovasc Surg* 1969; **58**: 62–70.

2 McKay R, Yacoub MH. Clinical and pathological findings in patients with "floppy" valves treated surgically. *Circulation* 1973; **47**, suppl 3: 63–73.

3 Salomon NW, Stinson EB, Griepp RB, Shumway NB. Surgical treatment of degenerative mitral regurgitation. *Am J Cardiol* 1976; **38**: 463–8.

4 Read RC, Thal AP, Wendt VE. Symptomatic valvular myxomatous transformation (the floppy valve syndrome): a possible forme fruste of the Marfan syndrome. *Circulation* 1965; **32**: 897–910.

5 Roberts WC, Perloff JK. Mitral valvular disease. A clinicopathologic survey of the conditions causing the mitral valve to function abnormally. *Ann Intern Med* 1972; **77:** 939–75.

6 Sherman EB, Char F, Dungan WT, Campbell GS. Myxomatous transformation of the mitral valve producing mitral insufficiency. *Am J Dis Child* 1970; **119:** 171–5.

7 McCarthy LJ, Wolf PL. Mucoid degeneration of heart valves: "blue valve syndrome". *Am J Clin Pathol* 1970; **54:** 852–6.

8 Pomerance A. Ballooning deformity (mucoid degeneration) of atrioventricular valves. *Br Heart J* 1969; **31:** 343–51.

9 Jamshidi A, Klein-Robbenhaar J. Myxomatous transformation of the aortic and mitral valve with subaortic "sail-like" membrane. *Am J Med* 1970; **49:** 114–7.

10 Pomerance A. Aging and degenerative changes. In: Pomerance A, Davies MJ, eds. *The pathology of the heart.* London: Blackwell Scientific Publication, 1975: 47–9.

11 Davis RH, Schuster B, Knoebel SB, Fisch C. Myxomatous degeneration of the mitral valve. *Am J Cardiol* 1971; **28:** 449–55.

12 Kern WH, Tucker BL. Myxoid changes in cardiac valves: pathological, clinical and ultrastructural studies. *Am Heart J* 1972; **84:** 294–301.

13 O'Brien KP, Hitchcock GC, Barratt-Boyes BG, Lowe JB. Spontaneous aortic cusp rupture associated with valvular myxomatous transformation. *Circulation* 1968; **37:** 273–8.

14 Bittar N, Sosa JA. The billowing mitral valve leaflet. Report on fourteen patients. *Circulation* 1968; **38:** 763–70.

15 Goodman D, Kimbiris D, Linhart JW. Chordae tendineae rupture complicating the systolic click-late systolic murmur syndrome. *Am J Cardiol* 1974; **33:** 681–4.

16 Jeresaty RM. Mitral valve prolapse-click syndrome. *Prog Cardiovasc Dis* 1973; **15:** 623–52.

17 Shrivastava S, Guthrie RB, Edwards JE. Prolapse of the mitral valve. *Mod Concepts Cardiovasc Dis* 1977; **46:** 57–61.

18 Marshall CE, Shappell SD. Sudden death and the ballooning posterior leaflet syndrome. Detailed anatomic and histochemical investigation. *Arch Pathol* 1974; **98:** 134–8.

19 Trent JK, Adelman AG, Wigle ED, Silver MD. Morphology of a prolapsed posterior mitral valve leaflet. *Am Heart J* 1970; **79:** 539–43.

20 Pomerance A. Aging changes in human heart valves. *Br Heart J* 1967; **29:** 222–31.

21 Procacci PM, Savran SV, Schreiter SI, *et al.* Prevalence of clinical mitral valve prolapse in 1169 young women. *N Engl J Med* 1976; **294:** 1086–8.

22 DeMaria AN, Amsterdam EA, Vismara LA, Neumann A, Mason DT. Arrhythmias in the mitral valve prolapse syndrome: prevalence, nature and frequency. *Ann Intern Med* 1976; **84:** 656–60.

23 Gooch AS, Vicencio F, Maranhao V, Goldberg N. Arrythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome. *Am J Cardiol* 1972; **29:** 611–20.

24 Swartz MH, Teicholz LE, Donoso E. Mitral valve prolapse: a review of associated arrhythmias. *Am J Med* 1977; **62:** 377–89.

25 Corrigall D, Bolen J, Hancock EW, Popp RL. Mitral valve prolapse and infective endocarditis. *Am J Med* 1977; **63:** 215–22.

26 Leichtman D, Nelson R, Gobel FL, Alexander CS, Cohn JN. Bradycardia with mitral valve prolapse: a potential mechanism of sudden death. *Ann Intern Med* 1976; **85:** 453–7.

27 Devereaux RB, Perloff JK, Reichek N, Josephson ME. Mitral valve prolapse. *Circulation* 1976; **54:** 3–14.

28 Salazar AE, Edwards JE. Friction lesions of ventricular endocardium: relation to chordae tendineae of mitral valve. *Arch Path* 1970; **90:** 364–376.

29 Feigenbaum H. *Echocardiography.* 2nd ed. Philadelphia: Lea and Feibinger, 1976.

30 Grossman W. *Cardiac catheterization and angiography.* Philadelphia: Lea and Feibinger, 1974.

31 Humphries WC Jr, Hammer WJ, Lemole G, McDonough MT, McCurdy RR, Spana JF Jr. Echocardiographic equivalents of a flail mitral leaflet. *Am J Cardiol* 1977; **40:** 802–7.

32 Rippe JM, Angoff G, Sloss LJ, Wynne J, Alpert IS. Multiple floppy valves: an echocardiographic syndrome. *Am J Med* 1979; **66:** 817–24.

33 Roberts WC, Virmani R. Aschoff bodies *at necroscopy* in valvular heart disease: evidence from an analysis of 543 patients over 14 years of age that rheumatic heart disease, at least anatomically, is a disease of the mitral valve. *Circulation* 1978; **57:** 803–7.

34 Torii S, Bashey RI, Nakao K. Acid mucopolysaccharide composition of human heart valve. *Biochim Biophys Acta* 1965; **101:** 285–91.

35 McKusick VA. *Heritable disorders of connective tissue.* 3rd ed. St. Louis: CV Mosby, 1966.

36 Dillon JC, Haine CL, Change S, Feigenbaum H. Use of echocardiography in patients with prolapsed mitral valve. *Circulation* 1971; **43:** 503–7.

37 Smith ER, Fraser DB, Purdy JW, Anderson RN. Angiographic diagnosis of mitral valve prolapse: correlation with echocardiography. *Am J Cardiol* 1977; **40:** 165–70.

38 DeMaria AN, Neumann A, Lee G, Mason DT. Echocardiographic identification of the mitral valve prolapse syndrome. *Am J Med* 1974; **62:** 819–29.

39 Popp RL, Brown OR, Silverman JF, Harrison DC. Echocardiographic abnormalities in the mitral valve prolapse syndrome. *Circulation* 1974; **49:** 428–33.

40 DeMaria AN, King JF, Bogren HG, Lies JE, Mason DT. The variable spectrum of echocardiographic manifestations of the mitral valve prolapse syndrome. *Circulation* 1974; **50:** 33–41.

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Incidence of coronary artery disease in patients with valvular heart disease

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SUMMARY The case notes, cardiac catheterisation data, and coronary arteriograms of 239 patients investigated for valvular heart disease during a five year period were reviewed. Angina was present in 13 of 95 patients with isolated mitral valve disease, 43 of 90 patients with isolated aortic valve disease, and 18 of 54 patients with combined mitral and aortic valve disease. Significant coronary artery disease was present in 85 per cent of patients with mitral valve disease and angina, but in only 33 per cent of patients with aortic valve disease and angina. Patients with no chest pain still had a high incidence of coronary artery disease, significant coronary obstruction being present in 22 per cent with mitral valve disease, 22 per cent with aortic valve disease, and 11 per cent with combined mitral and aortic valve disease. Several possible clinical markers of coronary artery disease were examined but none was found to be of practical help. There was, however, a significant inverse relation between severity of coronary artery disease and severity of valve disease in patients with aortic valve disease.

Asymptomatic coronary artery disease is not uncommon in patients with valvular heart disease and if it is policy to perform coronary artery bypass grafting in such patients, routine coronary arteriography must be part of the preoperative investigation.

Angina occurs commonly in valvular heart disease[1–8] but does not necessarily signify the presence of coronary artery disease,[1–3 8] This is particularly true in patients with aortic valve disease[1–8]; it also applies in those with mitral valve disease. In addition, there are some patients without angina who still have significant coronary obstruction.[3 8–10] In patients being considered for valve surgery it is generally accepted that the presence of angina is an indication for coronary arteriography as part of the preoperative investigations.[1 8 11–13] Much less is known of the need for routine coronary arteriography in patients without angina. Patients with coronary artery disease do less well after surgery,[11 13–17] and this has led to increasing interest in the possibility of treating coronary artery disease at the time of valve surgery. During the past five years it has been our policy to perform routine coronary arteriography on patients aged 45 years or more as part of the preoperative investigation, and coronary artery bypass grafting is performed for significant lesions whenever feasible, even when angina is absent. We have performed a retrospective study of these patients in order to answer three main questions. First, what is the incidence of significant coronary artery disease in patients with valve disease with and without angina? Second, are there any clinical features predictive of such disease? Third, how often are such lesions amenable to surgical correction?

Methods

We reviewed the case notes of all adult patients who underwent coronary arteriography as part of the preoperative cardiac catheterisation for valvular heart disease during the period 1 January 1975 to 31 December 1979. Patients with valvular heart disease resulting directly from ischaemic heart disease (for example papillary muscle dysfunction) were excluded. A note was made of each patient's age, sex, and smoking history. The clinical history was examined for evidence of angina pectoris. Episodes of typical anterior chest pain, with or without radiation, precipitated by exertion and relieved

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by rest or an oral nitrate, were regarded as "typical angina". In addition, there were some patients who had chest pain with some, but not all, of these features, and these were classified as "atypical chest pain". Patients without pain were classified as "no chest pain". A record was made of any past cardiac ischaemic events and past or current drug treatment. The electrocardiogram was examined for rhythm, evidence of cardiac ischaemia, and previous myocardial infarction. Heart size was assessed by the radiological cardiothoracic ratio.

The data obtained at cardiac catheterisation were reviewed. Pulmonary hypertension was indicated by a pulmonary artery mean pressure greater than 20 mmHg. Left ventricular end-diastolic pressure was measured directly. Mitral valve gradients were measured indirectly between pulmonary artery mean wedge pressure and left ventricular end-diastolic pressure. Aortic valve gradients were measured by withdrawal from left ventricle to aorta. Pressures were measured at rest using Statham (P23 Gp) strain gauges recording on an ultraviolet light recorder. The zero reference point was 10 cm above the level of the catheter table. The severity of valve obstruction was graded on a simple scale, from 0 to 4, according to the gradient at rest. For mitral stenosis: 0=no gradient; 1=1 to 4 mmHg; 2=5 to 10 mmHg; 3=11 to 19 mmHg; 4=more than 20 mmHg. For aortic stenosis: 0=no gradient; 1=1 to 34 mmHg; 2=35 to 49 mmHg; 3=50 to 74 mmHg; 4=more than 75 mmHg. Haemodynamically "significant" valve obstruction was arbitrarily defined as grade 3 or 4. The severity of mitral or aortic valve regurgitation was assessed from the left ventricular or aortic root cine angiogram and graded on a simple scale from 0 to 4 according to the criteria of Yang *et al.*[18] Haemodynamically "significant" regurgitation was said to be present with a grade of 3 or 4. The overall severity of valvular disease was assessed by summing all the grades of stenosis and regurgitation, this then being called the valve score. On the basis of the data obtained from cardiac catheterisation and angiography the patients were assigned to one of three groups, depending upon the presence of "significant" disease as defined above: isolated mitral valve disease; isolated aortic valve disease; combined mitral and aortic valve disease.

Left ventricular function was assessed from the ejection fraction, calculated from the left ventricular volumes obtained from single plane right anterior oblique ventriculography.[19] Coronary arteriography was performed by the Judkins or Sones technique. Both coronary arteries were injected in at least three projections using magnified images. The arteriograms were analysed by a cardiac radiologist and at least one other experienced operator. In the case of borderline lesions, or a disparity in reporting, a third opinion was obtained. All reporting was done without clinical knowledge of the patient. The severity of coronary artery stenosis was assessed as the maximum percentage reduction in luminal diameter, seen in any one of at least three different projections, as compared with the diameter of the vessel proximal to the obstruction. The severity of each lesion was graded on a simple scale from 0 to 4 as follows: 0=no obstruction; 1=1 to 49 per cent; 2=50 to 69 per cent; 3=70 to 99 per cent; 4=total occlusion. Obstructions of grade 2 or more were said to be "significant". The maximum narrowings on five major vessels' branches were assessed. The left main stem; left anterior descending; circumflex; obtuse marginal (large lateral) branch of the circumflex; and right coronary arteries were chosen because of their surgical importance in coronary artery bypass grafting. Major vessel disease was assessed as zero, single, double, or triple, and the overall severity of coronary artery disease was estimated by summing the grades of stenosis in the five vessel branches listed above. This total was called the coronary score.

Finally the decision made at the time of investigation regarding surgery was recorded and the operation notes examined to obtain details of the procedure performed.

The significance of differences between groups was tested using Student's t test for unpaired data or χ^2 as appropriate. The significance of correlations was tested by linear regression analysis.

Results

During the study period, 239 patients with valvular heart disease underwent routine coronary arteriography as part of their preoperative cardiac catheterisation. Isolated mitral valve disease was present in 95 (40%) with isolated stenosis in 35 and isolated regurgitation in 10, the remaining 50 having mixed lesions. Isolated aortic valve disease was present in 90 (38%) with isolated stenosis in 37, isolated regurgitation in 28, and mixed lesions in 25. There were 54 (23%) patients with combined mitral and aortic valve disease. A few patients also had tricuspid valve disease but the severity of this was not assessed. The average age of the patients was 51·0 ± 8·7 years (±SD), with no differences between the valve groups. There were 117 men and 122 women. Typical angina was present in 74 (31%) patients, atypical chest pain in 34 (14%), and no chest pain in 131 (55%). Coronary arteriography was therefore performed as a routine screening procedure in more than half the patients.

Table 1 *Relation between angina and coronary artery disease in 239 patients being investigated for valvular heart disease*

Nature of chest pain	*No. of patients*	*No. (%) of patients with coronary lesions*						
		No significant disease			*Significant disease*			
		No irregularity	*1 to 49% occlusion*	*Total*	*Single vessel*	*Double vessel*	*Triple vessel*	*Total*
Angina	74	29 (39)	12 (16)	41 (55)	17 (23)	11 (15)	5 (7)	33 (45)
Atypical chest pain	34	16 (47)	8 (24)	24 (71)	6 (18)	0 (0)	4 (12)	10 (29)
No chest pain	131	64 (49)	41 (31)	105 (80)	13 (10)	7 (5)	6 (5)	26 (20)

Coronary arteriography disclosed at least one major vessel with significant narrowing in 69 (29%) patients, but in 109 (46%) there was not even minimal irregularity. Details of the relation between the incidence of angina and the incidence of coronary artery disease overall are given in Table 1. Significant coronary lesions were present in 33 of 74 (45%) patients with angina and in 26 of 131 (20%) patients with no chest pain. On the other hand, in 26 of 69 (38%) patients with significant coronary artery obstruction there was no clinical suspicion of angina. The distribution of lesions in the five major vessel branches examined is shown in Table 2. In the next part of the study the relation between chest pain and coronary artery disease in each of the three valve groups was examined.

ISOLATED MITRAL VALVE DISEASE (Table 3)

Typical angina was present in 13 (14%) patients of whom 11 (85%) had significant coronary lesions, four having triple vessel disease. Of the 63 (66%) patients with no chest pain, 14 (22%) had significant coronary lesions, four with triple vessel disease. Of the 35 patients with isolated mitral stenosis, only three (9%) had angina and all of these had significant coronary lesions. Of the 22 (63%) patients with isolated stenosis and no chest pain, five (23%) proved to have significant coronary disease.

ISOLATED AORTIC VALVE DISEASE (Table 3)

Typical angina was present in 43 (48%) patients of whom 14 (33%) had significant coronary lesions, one with triple vessel disease. Of the 41 (46%) patients with no chest pain, nine (22%) had significant coronary lesions, two with triple vessel disease. Of the 37 patients with isolated aortic stenosis, angina was present in 23 (62%) of whom nine (39%) had significant coronary artery disease. Twelve (32%) of the patients with isolated aortic stenosis had no chest pain but three (25%) had significant coronary lesions.

COMBINED MITRAL AND AORTIC VALVE DISEASE (Table 3)

Typical angina was present in 18 (33%) patients of whom eight (44%) had significant coronary lesions, but none with triple vessel disease. Of the 27 (50%) patients with no chest pain, three (11%) had significant coronary lesions, none with triple vessel disease.

In all three groups angina was therefore more likely to be associated with significant coronary artery disease than when chest pain was absent. Only in patients with isolated mitral valve disease, however, was angina a very good marker of significant coronary obstruction. Other factors were therefore examined which might possibly help to identify patients with coronary artery disease.

Table 2 *Distribution and severity of coronary artery disease in 239 patients being investigated for valvular heart disease*

Maximum per cent reduction in luminal diameter	*No. (%) of patients with coronary artery lesions*				
	Left main stem	*Left anterior descending coronary artery*	*Circumflex coronary artery*	*Obtuse marginal**	*Right coronary artery*
0	227 (95)	161 (67)	178 (75)	206 (86)	148 (62)
1–49	10 (4)	36 (15)	34 (14)	14 (6)	57 (24)
50–69	2 (1)	20 (8)	13 (5)	3 (1)	14 (6)
70–99	0 (0)	20 (8)	13 (5)	16 (7)	15 (6)
100	0 (0)	2 (1)	1 (0·5)	0 (0)	5 (2)

*Or large lateral branch of the circumflex.

NATURE OF VALVE LESION

The mean ($\pm$SEM) coronary scores for each valve group were as follows: isolated mitral valve disease $= 2\cdot 82 \pm 0\cdot 37$, isolated aortic valve disease $= 1\cdot 78 \pm 0\cdot 26$, combined mitral and aortic valve disease $= 1\cdot 45 \pm 0\cdot 27$. The severity of coronary artery disease was therefore greater in patients with mitral valve disease than with aortic valve disease ($p < 0\cdot 05$) or combined aortic and mitral valve disease ($p < 0\cdot 01$), there being no difference between the two latter.

SEVERITY OF VALVULAR DISEASE

The mean ($\pm$SEM) valve scores for each group were as follows: isolated mitral valve disease $= 4\cdot 17 \pm 0\cdot 21$, isolated aortic valve disease $= 3\cdot 84 \pm 0\cdot 21$, combined mitral and aortic valve disease $= 6\cdot 88 \pm 0\cdot 28$. There was no significant difference between mitral and aortic valve disease, but, by virtue of having two valves affected, patients with combined mitral and aortic valve disease had higher scores ($p < 0\cdot 001$). Because the group with the highest mean valve score (the combined group) had both the lowest incidence and also the lowest overall severity of coronary artery disease (mean coronary score), it was decided to study the relation between these factors in more detail. In each group there was a negative relation between valve score and coronary score but this was of statistical significance only in patients with isolated aortic valve disease ($p < 0\cdot 05$).

PRESENCE OF ANGINA

As shown above, angina was not a good marker of the presence of significant coronary lesions. It was least good in patients with isolated aortic stenosis and best in isolated mitral stenosis. The mean ($\pm$SEM) coronary scores for those patients with angina were compared with those having no chest pain in each valve group. Though patients with angina tended to have higher mean coronary scores ($\pm$SEM), this was only significant for patients with isolated mitral valve disease (angina $= 5\cdot 9 \pm 1\cdot 2$, no chest pain $= 2\cdot 0 \pm 0\cdot 3$; $p < 0\cdot 001$).

AGE

In all three groups coronary scores tended to increase with age and the correlation was significant for patients with isolated mitral valve disease ($p < 0\cdot 01$) and combined mitral and aortic valve disease ($p < 0\cdot 025$). Though patients aged below 45 years did not have routine coronary arteriography it was performed in 41. The indication for this was the presence of angina in 13 of whom three had significant coronary obstruction. None of the 23 patients with no chest pain had significant coronary lesions.

SMOKING

Of the 239 patients, 129 (54%) were habitual cigarette smokers. Though smokers tended to have significant coronary lesions more frequently, and higher mean coronary scores ($\pm$SEM), the differences did not reach levels of statistical significance (mean coronary score for smokers $2\cdot 31 \pm 0\cdot 26$, for non-smokers $1\cdot 84 \pm 0\cdot 28$; $p < 0\cdot 1$).

SEX

The mean ($\pm$SEM) coronary score for men tended to be higher than for women but the differences were only of statistical significance for isolated mitral valve disease (men $= 4\cdot 27 \pm 0\cdot 72$, women $= 2\cdot 22 \pm 0\cdot 42$; $p < 0\cdot 02$).

Table 3 *Relation between angina and coronary artery disease in patients with isolated mitral valve disease, isolated aortic valve disease, and combined mitral and aortic valve disease*

Nature of chest pain	*No. of patients*	*No. (%) of patients with coronary artery lesions*						
		No significant disease			*Significant disease*			
		No irregularity	*1 to 49% occlusions*	*Total*	*Single vessel*	*Double vessel*	*Triple vessel*	*Total*
		Isolated mitral valve disease						
Angina	13	1 (8)	1 (8)	2 (15)	5 (38)	2 (15)	4 (31)	11 (85)
Atypical chest pain	19	11 (58)	2 (11)	13 (68)	2 (11)	0 (0)	4 (21)	6 (32)
No chest pain	63	23 (37)	26 (41)	49 (78)	7 (11)	3 (5)	4 (6)	14 (22)
		Isolated aortic valve disease						
Angina	43	20 (47)	9 (21)	29 (67)	6 (14)	7 (16)	1 (2)	14 (33)
Atypical chest pain	6	2 (33)	2 (33)	4 (67)	2 (33)	0 (0)	0 (0)	2 (33)
No chest pain	41	27 (66)	5 (12)	32 (78)	5 (12)	2 (5)	2 (5)	9 (22)
		Combined mitral and aortic valve disease						
Angina	18	8 (44)	2 (11)	10 (56)	6 (33)	2 (11)	0 (0)	8 (44)
Atypical chest pain	9	3 (33)	4 (44)	7 (78)	2 (22)	0 (0)	0 (0)	2 (22)
No chest pain	27	14 (52)	10 (37)	24 (89)	1 (4)	2 (7)	0 (0)	3 (11)

LEFT VENTRICULAR END-DIASTOLIC PRESSURE, CARDIOTHORACIC RATIO, EJECTION FRACTION, MEAN PULMONARY ARTERY PRESSURE

The relations between coronary score, and left ventricular end-diastolic pressure, cardiothoracic ratio, ejection fraction, and mean pulmonary artery pressure were small and inconsistent. Furthermore, there were no significant differences between patients with coronary scores greater than 6 and those with no coronary lesions. Nor were there any differences in the incidence of angina or coronary artery disease between those patients with and without pulmonary hypertension, but mean pulmonary artery pressure was usually only mildly increased and only 10 patients had levels more than 50 mmHg.

MULTIPLE REGRESSION ANALYSIS OF FACTORS PREDICTIVE OF CORONARY SCORE

As many of the factors described above are likely to be interrelated a multiple regression analysis was performed to identify which were independently predictive of the coronary score. In patients with isolated mitral valve disease, age in the presence of angina was predictive ($p < 0{\cdot}005$), and age in patients with combined mitral and aortic valve disease ($p < 0{\cdot}025$). None of the factors was predictive in patients with isolated aortic valve disease.

SURGICAL MANAGEMENT

Isolated mitral valve disease

Seventy-one patients had valve surgery. Significant coronary obstruction was present in 18 (25%) but the vessels were angiographically suitable for coronary artery bypass grafts in only 14. Eventually 18 grafts were performed in 13 patients. Coronary artery surgery was performed in seven (11%) of the original 63 patients with isolated mitral valve disease but no chest pain, representing 13 per cent of such patients coming to surgery.

Isolated aortic valve disease

Sixty-nine patients had valve surgery. Significant coronary obstructions were present in 21 (30%) and the vessels were angiographically suitable for coronary artery bypass grafts in 20 (29%). Eventually 30 grafts were performed in the 20 patients. Coronary artery surgery was performed in three (7%) of the original 41 patients with isolated aortic valve disease and no chest pain, representing 10 per cent of such patients coming to surgery.

Combined mitral and aortic valve disease

Forty-six patients had surgery. Significant coronary obstructions were present in nine (20%) with the vessels angiographically suitable for coronary artery bypass grafts in all of these. Eventually eight grafts were performed in eight patients. Coronary artery surgery was performed in two (7%) of the original 27 patients with combined mitral and aortic valve disease and no chest pain, representing 8 per cent of such patients coming to surgery.

Discussion

The first part of this study was designed to determine the incidence of angina and coronary artery disease in patients undergoing investigation for valvular heart disease. As in a previous study[1] angina was much commoner in the presence of aortic valve disease (48%) than in mitral valve disease (14%). The incidence of angina was greatest in those with isolated aortic stenosis (62%) and least in those with isolated mitral stenosis (9%). Previous reports of angina in association with isolated aortic valve disease have reported incidences between 45 and 70 per cent.[1–8] Most studies have been of patients with isolated aortic stenosis, though there seems to be little difference in the incidence of angina between those patients with predominant stenosis and those with predominant regurgitation.[1 2] In this study, angina was more frequent in the presence of predominant stenosis.

Compared with aortic valve disease, little attention has been given to the incidence of angina in patients with isolated mitral valve disease, possibly because it was thought to be relatively uncommon. Baxter *et al.*,[1] however, reported 33 per cent of such patients with angina, a higher figure than that reported here (14%), but much must depend upon the criteria used in making a clinical diagnosis of angina. Baxter *et al.* do not state their criteria and, not having a separate group with atypical chest pain, such patients may have been included in their angina group. It is clear, however, that angina can occur in association with mitral valve disease (even isolated mitral stenosis) and the incidence in this study is higher than that of 5·5 per cent previously reported for a general population of similar age distribution.[20] The incidence of angina in patients with combined mitral and aortic valve disease (33%) was intermediate between the two other valve groups.

There are several reasons why angina might show an increased incidence in the presence of valvular heart disease.[21] Aortic valve disease is associated with increased left ventricular wall tension and myocardial oxygen requirement, while coronary blood flow and perfusion gradient may be decreased. In mitral stenosis, angina may result from low cardiac output and decreased coronary perfusion, but our findings suggest that in the presence of this lesion it is more likely to be associated with severe coronary artery disease than it is in aortic valve disease. In this study pulmonary hypertension did not predispose to angina, but pulmonary pressure was severely raised in only a small number of patients.

In contrast to the symptom of angina, the incidence of significant coronary lesions was highest in isolated mitral valve disease (33%) and lowest in isolated aortic valve disease (28%). Comparison with previous studies is hindered by differences in the criteria used to classify a lesion as "significant". In this study, luminal narrowing of < 50 per cent was used, as our surgical policy is to graft such vessels if possible. When similar criteria have been used by others in patients with aortic valve disease, significant lesions were found in fewer patients (17%).[1] Other reports, taking 75 per cent narrowing as "significant", show an incidence of coronary artery disease of 14 per cent[2] and 23 per cent.[3] Swanton *et al.*[8] reported 23 per cent of patients with isolated aortic valve disease as having "significant" coronary lesions, but did not state the criteria used.

There have been few angiographic studies of the coronary arteries in patients with isolated mitral valve disease. Baxter *et al.*[1] reported lesions greater than 50 per cent narrowing in 22 per cent of patients. In isolated mitral stenosis significant coronary lesions have been reported in 18 per cent of patients at angiography[22] and in 32 per cent at necropsy.[23] In the present study 33 per cent of patients with mitral valve disease had at least one major coronary obstruction, thus confirming the substantial incidence of concomitant coronary artery disease in these patients.

Not only did patients with mitral valve disease have significant coronary lesions more frequently than those with aortic valve disease, but the overall severity (as assessed by the coronary score) was greater. It is not clear, however, whether mitral valve disease predisposes to coronary artery disease or whether aortic valve disease is relatively protective. It has been suggested that the rheumatic process induces coronary disease[24] but necropsy evidence disagrees.[25] Nakib *et al.*[26] suggest that in the presence of aortic stenosis, the severity of coronary artery disease is inversely related to the valve gradient, supporting a protective mechanism.

As a possible relation may exist between severity of coronary artery disease and severity of valve disease, an attempt was made to correlate an index of severity of valve disease (valve score) with one of the severity of coronary artery disease (coronary score). The group with the highest valve score (combined mitral and aortic valve disease) had the lowest coronary score but the converse did not hold. Valve score and coronary score had an inverse relation in all groups but this was only of statistical significance in patients with isolated aortic valve disease. The method used is arbitrary and does not take into account other factors, such as cardiac output, but nevertheless it appears that coronary artery disease may contribute to the severity of symptoms in patients with valvular heart disease. Further, clinical deterioration leading to consideration of valve surgery may be the result in part of increasing severity of coronary artery disease rather than deterioration caused by the valve itself. Identification of coronary disease must therefore become an important part of preoperative investigation, and its alleviation a consideration in any surgical intervention.

If this is accepted, how can identification of coronary artery disease be achieved? Taking angina as a marker of coronary artery disease our findings agree with previous studies,[1–4 12] where angina in aortic valve disease indicates significant coronary lesions in only 33 per cent of patients. Angina in mitral valve disease is more significant, 85 per cent of such patients having major coronary obstruction. In this series, all patients with isolated mitral stenosis and angina had significant coronary artery disease. While angina is a poor marker of coronary artery disease in aortic valve disease, in mitral valve disease it is valuable. An absence of angina is less useful. The substantial incidence (22%) of significant coronary disease in patients with aortic valve disease but no chest pain in the present study confirms that the absence of chest pain in isolated aortic valve disease does not rule out the presence of significant coronary artery disease. The figures for mitral valve disease without chest pain are similar.

In the second part of this study other factors, possibly predictive of the presence of coronary artery disease, were examined. Though men tended to have more severe coronary artery disease than women, the difference was significant only in isolated mitral valve disease. The severity of coronary artery disease increased with age but there was no age below which it could be confidently excluded. No significant differences were found between smokers and non-smokers. Surprisingly, there was no significant relation between severity of coronary artery disease and several simple indices of left ventricular function. Previous studies have shown that the resting electrocardiogram is also of little value.[1 10] In a multiple regression analysis of these factors only angina and age in patients with isolated mitral valve disease, and age in patients with mitral and aortic valve disease, were predictive of the severity of coronary artery disease. It therefore seems clear that, if it is desirable to identify patients with coronary artery obstructions before valve surgery, there is no simple alternative to routine coronary arteriography. We have no data to set a lower age limit for this recommendation. Though coronary artery disease was found in patients aged below 45 years, coronary arteriography was not performed as a routine procedure in this group.

A remaining question is whether significant coronary artery disease, if found, should be treated by coronary artery bypass grafts. Coronary artery disease may contribute to symptoms before and after valve surgery and the mortality of surgery may thus be considerably influenced. Poor results have been attributed to uncorrected coronary artery disease,[11 13–15] with twice the perioperative mortality of patients with no coronary artery disease.[27] Long-term survival is also reduced.[16] Previous reports of aortic valve replacement with concomitant coronary artery bypass grafts have suggested higher,[13 28–31] lower,[27 32 33] or unchanged[16 34 35] mortality as compared with aortic valve replacement alone. In all except one of these studies,[32] coronary artery bypass graft was performed immediately after valve replacement, inferring that during the phase of valve replacement the distal myocardium was at risk from underperfusion. Macmanus *et al.*[32] report a comparison of patients treated in this sequence with a group treated in the reverse order and suggest that coronary artery bypass grafting performed first reduces the risk of operative myocardial infarction. In the present series the overall perioperative (within four weeks) mortality of valve replacement combined with coronary artery bypass graft was 20 per cent compared with 5·9 per cent for valve replacement alone. Patients undergoing coronary artery bypass grafts, however, represent a group with increased risk by virtue of their coronary artery disease and to make true comparisons of perioperative mortality and the degree of postoperative improvement it would be necessary to carry out a randomised prospective trial of patients with similar degrees of valvular and coronary disease.

In conclusion, this study has shown that asymptomatic coronary artery disease is common in patients undergoing assessment for valve surgery and that there are no adequate clinical markers for such coronary lesions. We therefore believe that routine coronary arteriography is necessary for proper diagnosis in patients with valvular heart disease before surgery. The yield of significant coronary lesions has been shown to average 33 per cent in patients aged 45 years or over but we have no data as to the incidence in lower age groups.

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References

1 Baxter RH, Reid JM, McGuiness JB, Stevenson JG. Relation of angina to coronary artery disease in mitral and aortic valve disease. *Br Heart J* 1978; **40**: 918–22.

2 Basta LL, Raines D, Najjar S, Kioschos JM. Clinical, haemodynamic and coronary angiographic correlates of angina pectoris in patients with severe aortic valve disease. *Br Heart J* 1975; **37**: 150–7.

3 Harris CN, Kaplan MA, Parker DP, Dunne EF, Cowell HS, Ellestad MH. Aortic stenosis, angina, and coronary artery disease: interrelations. *Br Heart J* 1975; **37**: 656–61.

4 Mandal AB, Gray IR. Significance of angina pectoris in aortic valve stenosis. *Br Heart J* 1976; **38**: 811–5.

5 Lewes D. Diagnosis of aortic stenosis. Based on a study of 25 proved cases. *Br Med J* 1951; **i**: 211–6.

6 Wood P. Aortic stenosis. *Am J Cardiol* 1958; **1**: 553–71.

7 Baker C, Somerville J. Clinical features and surgical treatment of fifty patients with severe aortic stenosis. *Guys Hospital Reports* 1959; **108**: 101–25.

8 Swanton RH, Brooksby IAB, Jenkins BS, *et al.* Determinants of angina in aortic stenosis and the importance of coronary arteriography. *Br Heart J* 1977; **39**: 1347–52.

9 Moraski RE, Russell RO Jr, Mantle JA, Rackley CE. Aortic stenosis, angina pectoris, coronary artery disease. *Cathet Cardiovasc Diagn* 1976; **2**: 157–64.

10 Lacy JP, Goodin RR, Flowers NC. Coronary atherosclerosis in valvular heart disease: the need for coronary arteriography (abstract). *Am J Cardiol* 1975; **35**: 151.

11 Linhart JW, Wheat MW Jr. Myocardial dysfunction following aortic valve replacement. The significance of coronary artery disease. *J Thorac Cardiovasc Surg* 1967; **54**: 259–69.

12 Bonchek LI, Anderson RP, Rösch J. Should coronary arteriography be performed routinely before valve replacement? *Am J Cardiol* 1973; **31**: 462–6.

13 Loop FD, Phillips DF, Roy M, Taylor PC, Groves LK, Effler DB. Aortic valve replacement combined with myocardial revascularisation. *Circulation* 1977; **55**: 169–73.

14 Sharratt GP, Rees P, Conway N, Myocardial infarction complicating aortic valve replacement. *J Thorac Cardiovasc Surg* 1976; **71**: 869–71.

15 Fishman NH, Youker JE, Roe BB. Mechanical injury to the coronary arteries during operative cannulation. *Am Heart J* 1968; **75**: 26–33.

16 Richardson JV, Kouchoukos NT, Wright JO III, Karp RB. Combined aortic valve replacement and myocardial revascularisation: results in 220 patients. *Circulation* 1979; **59**: 75–81.

17 Roberts WC, Morrow AG. Late postoperative

pathological findings after cardiac valve replacement. *Circulation* 1967; **35** & **36,** suppl I: 48–62.

18 Yang SS, Bentivoglio LG, Maranhão V, Goldberg H. *From cardiac catheterisation data to haemodynamic parameters*. Philadelphia: F A Davis, 1972.

19 Kasser IS, Kennedy JW. Measurement of left ventricular volumes in man by single-plane cineangiocardiography. *Invest Radiol* 1969; **4:** 83–90.

20 Erikssen J, Enge I, Forfang K, Storstein O. False positive diagnostic tests and coronary angiographic findings in 105 presumably healthy males. *Circulation* 1976; **54:** 371–6.

21 Anonymous. Angina and aortic valve stenosis. *Br Med J* 1977; **i:** 597–8.

22 Befeler B, Kamen AR, MacLeod CA. Coronary artery disease and left ventricular function in mitral stenosis. *Chest* 1970; **57:** 435–9.

23 Tadavarthy SM, Vlodaver Z, Edwards JE. Coronary atherosclerosis in subjects with mitral stenosis. *Circulation* 1976; **54:** 519–21.

24 Zeek P. Studies in atherosclerosis. I. Conditions in childhood which predispose to the early development of arteriosclerosis. *Am J Med Sci* 1932; **184:** 350–6.

25 Gardner FE, White PD. Coronary occlusion and myocardial infarction associated with chronic rheumatic heart disease. *Ann Intern Med* 1949; **31:** 1003–9.

26 Nakib A, Lillehei CW, Edwards JE. The degree of coronary atherosclerosis in aortic valvular disease. *Arch Pathol* 1965; **80:** 517–20.

27 Copeland JG, Griepp RB, Stinson EB, Shumway NE. Long-term follow-up after isolated aortic valve replacement. *J Thorac Cardiovasc Surg* 1977; **74:** 875–89.

28 Berndt TB, Hancock EW, Shumway NE, Harrison DC. Aortic valve replacement with and without coronary artery bypass surgery. *Circulation* 1974; **50:** 967–71.

29 Rossiter SJ, Hultgren HN, Koesk JC, Wuerflein RD, Angell WW. Ischemic myocardial injury with aortic valve replacement and coronary bypass. *Arch Surg* 1974; **109:** 652–8.

30 Loop FD, Favaloro RG, Shirey EK, Groves LK, Effler DB. Surgery for combined valvular and coronary heart disease. *JAMA* 1972; **220:** 372–6.

31 Anonymous. Coronary arteriography before aortic valve replacement. *Br Med J* 1979; **i:** 1443–4.

32 Macmanus Q, Grunkemeier G, Lambert L, Dietl C, Starr A. Aortic valve replacement and aortocoronary bypass surgery. Results with perfusion of proximal and distal coronary arteries. *J Thorac Cardiovasc Surg* 1978; **75:** 865–9.

33 Ross JK, Monro JL, Manners JM, *et al.* Cardiac surgery in Wessex: review of 1000 consecutive open heart procedures. *Br Med J* 1976; **ii:** 1485–9.

34 Riner RN, Tajik AJ, Wallace RB, Frye RL. Aortic valve replacement and myocardial revascularisation: early mortality (abstract). *Am J Cardiol* 1979; **41:** 412.

35 Merin G, Danielson GK, Wallace RB, Rutherford BD, Fluth JR. Combined one-stage coronary artery and valvular surgery. *Circulation* 1975; **47** & **48,** suppl III: 173–6.

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Br Heart J 1980; **44:** 638–49

Physical training after heart valve replacement

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SUMMARY A controlled trial was undertaken to examine the efficacy of physical training in patients recovering from the replacement of a single heart valve.

Patients were allocated to a test or control group two weeks after operation. Each patient performed a submaximal exercise test at entry, and 12 and 24 weeks after this test. The Canadian Air Force exercise programme was undertaken by the test group, while the control group continued normal activities for the 24 weeks between the first and last exercise group.

A regression line of submaximal heart rate on oxygen consumption was calculated from the data of each exercise test in each patient. Alterations in this line were used as an "index" of changes in "cardiorespiratory fitness".

The individual results showed a consistent improvement in "cardiorespiratory fitness" over the first 12 weeks in both groups. Only patients in the test group continued to improve between 12 and 24 weeks. Thus the exercise programme modified the recovery of "cardiorespiratory fitness" after operation.

Results in patients who developed clinical complications, and were excluded from the trial, predicted a deteriorating clinical condition.

This finding suggested that sequential exercise tests are of value after cardiac surgery.

In recent years considerable interest has been shown in the physical rehabilitation of patients suffering from ischaemic heart disease and rehabilitation programmes for these patients are an integral feature of the health service of many countries. In contrast, physical training in patients with other forms of cardiac disease, particularly those undergoing surgery for valvular diseases of the heart, has received little attention.[1] A programme of physical training for these patients could be justified readily, however, from the known effects of training and bed-rest on cardiorespiratory fitness.

Patients commonly present for valve surgery after years of partial, or even complete, impairment of physical activity. Cardiorespiratory fitness will be further impaired by surgical trauma and postoperative bed-rest.[2 3] Therefore, patients recovering from, albeit successful, cardiac surgery are not in an optimum state of cardiorespiratory fitness,[4] especially after mitral valve replacements and in patients in whom a valve lesion is caused by rheumatic heart disease known to impair cardiac performance.[5 6] Such a proposition is supported by the observation that haemodynamic improvement (as defined by catheter studies made at rest) is not reflected in comparable "functional" improvement.[7 8]

The present study was undertaken to establish the efficacy of physical training in patients recovering from the replacement of a single heart valve. A suitable training programme, and an exercise test which provides a valid index of cardiorespiratory fitness have been examined and the results reported previously.[9]

Subjects and method

(1) SELECTION OF 24 PATIENTS FOR STUDY

Only patients who had undergone a single heart valve replacement (aortic or mitral) were considered for entry to the trial. Two weeks after operation these patients were assessed by a cardiologist (JBS) who, with supportive evidence from certain laboratory investigations (for example blood urea, haemoglobin, $FEV_1\%$) adjudged them to be a "satisfactory operative result". Clinical criteria adopted in reaching this decision were the *absence* of: (a) angina pectoris, (b) significant murmurs, (c) clinical signs of heart failure, (d) anaemia, (e)

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significant pulmonary and renal disease, and (f) significant joint disease or other disabilities preventing an exercise test.

Patients who had been admitted in atrial fibrillation which was controlled with digoxin after operation were considered for entry to the trial. Patients maintained on antiarrhythmic agents after operation were excluded. Only patients who gave their formal consent to undergo a sequence of postoperative exercise tests on a bicycle ergometer were accepted for the study. The procedure for this investigation was approved by the hospital ethical committee.

At entry to the trial, the patients were allocated to a trial group or to a control group solely according to convenience of travel as determined by domicile; all patients lived and worked within the West Yorkshire industrial conurbation.

(2) PROCEDURE FOR TRIAL

Exercise tests were performed on all patients between two and three weeks after operation, and then 12 and 24 weeks after this first test, when the clinical progress of each patient was also reviewed. After their first exercise test patients in the test group undertook the training programme for 24 weeks.

(3) EXERCISE TEST

In each test, an attempt was made to obtain a relation between the heart rate and the oxygen consumption for a series of submaximal work loads.

(a) *Procedure*

All patients were tested at least two hours after their most recent meal. After sitting or lying quietly for 15 to 20 minutes they mounted an electrically braked bicycle ergometer (Elema Schonander, Type 380) and the procedure was explained to them. Saddle height was set at maximum comfortable leg extension and remained unchanged for each patient on subsequent retesting. After the attachment of electrocardiograph electrodes patients remained seated on the bicycle ergometer for five to 10 minutes in order to obtain a steady "initial heart rate". Any electrocardiographic abnormalities present at rest were recorded.

Usually six submaximal work loads were presented to each patient. These were arranged in three pairs in a discontinuous but increasing series as illustrated in Fig. 1. Each work load was pedalled for a nominal five to six minutes at 60 rpm until the criteria for a steady state, as defined below, was achieved. The heart rate and the oxygen consumption were then measured. Rest periods between loads were not fixed but prolonged until the recovery heart rate was within five to 10 per cent of the initial heart rate.

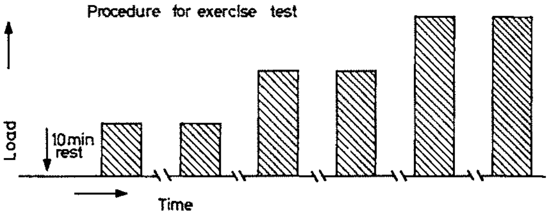

Fig. 1 *Exercise test procedure. Relative changes in work load are represented on the vertical axis. These changes are related to time on the horizontal axis. Subjects mounted the bicycle ergometer at time indicated by the arrow.*

Work loads were selected to obtain an increase in the exercise heart rate of 50 to 70 beats/min over the complete test, to permit adequate definition of the heart rate/oxygen consumption (HR/$\dot{V}o_2$) relation without departure from linearity. Thus the work loads used differed between patients but were usually 200, 300, and 400 kpm/min (32·8, 49·2, 65·6 W) for women, and 200, 400 and 600 kpm/min (32·8, 65·6, 98·4 W) for men. In some patients, an increase in exercise heart rate of 30 to 40 beats/min was accepted as the first postoperative test and an initial work load of 100 kpm/min (16·4 W) selected.

Laboratory ventilation was assisted by wall mounted fans and all patients exercised in an ambient temperature of 19 to 22°C, humidity 45 to 60 per cent. Oxygen consumption was measured continuously during exercise by an open circuit "flow through" technique which has been described previously.[10] This technique is free from systematic error and its random error (that is 95% tolerance limits) is 4 per cent. This apparatus provided a direct digital display of oxygen consumption in cm^3/min. The output was also amplified (EMMA system, SE Laboratories, Feltham, Middlesex) and recorded on an ultraviolet recorder (Model 2100, SE Laboratories).

This method was particularly suitable for measuring "steady state" values of submaximal oxygen consumption since the approach and attainment of a steady state of oxygen consumption was readily assessed as a plateau in the tracing on the ultraviolet recorder. All values of oxygen consumption were expressed at 20°C and 760 mmHg (101·1 kPa).

The electrocardiogram was recorded alongside the tracing of the oxygen consumption. The heart rate was determined by counting cardiac cycles over at least one minute during the "steady state" of oxygen consumption. An additional output from the electrocardiographic amplifier was used to drive a cardiotachometer (Type 4913, SE Laboratories) to provide a continuous display of the heart rate.

Criteria for the achievement of a "steady state" were therefore: (i) a sustained "plateau" of oxygen consumption for at least one minute ($<5\cdot0\%$ variation); and (ii) a sustained and concurrent steady heart rate ($<2\cdot0\%$ variation).

(b) *Patient monitoring and safety*
All exercise tests were carried out by two medically qualified staff. The electrocardiogram of each patient was continually displayed on a memory oscilloscope (Model 434–1 SE Laboratories) permitting the retention of any electrocardiographic abnormalities during exercise. Full resuscitation facilities were available including a wall mounted DC defibrillator (Model 282, Cardiac Recorders Ltd). Exercise tests were terminated at the onset of any of the following symptoms and signs: dyspnoea, pain, arrhythmia, and conduction disturbance.

(4) TRAINING PROGRAMME

All patients in the test group followed the Royal Canadian Air Force exercise programme, 5BX for men and XBX for women,[9 11] which has been recommended for sedentary normal subjects. This programme was considered particularly suitable since it is well defined in terms of its frequency, duration, and age related rate of progression. As it required only 11 to 12 minutes of daily exercise we expected good patient adherence. This time was split in approximately equal proportions between muscle strengthening exercises (callisthenics) and a stationary run. The frequency of each exercise is increased with progression of training to keep within the set time. The efficacy of this training programme in improving the cardiorespiratory fitness of normal subjects has been established previously.[9] In addition, the short duration of the exercise sequences causes minimal interference with normal activities and since no special equipment is required it can be undertaken at home.

(5) TRAINING SCHEDULE FOR TEST GROUP

(a) *First three weeks*
Patients attended the physiotherapy department on five days a week and training was supervised by a qualified physiotherapist. This ensured that each patient was fully conversant with the timing and duration of the exercise sequences. Medical staff recorded the electrocardiogram before and after exercise and the heart rate over the first 20 seconds of recovery.

(b) *Three to 13 weeks*
Patients attended the physiotherapy department for supervised training twice a week. On the remaining five days training was continued unsupervised at home.

(c) *Thirteen to 24 weeks*
Patients trained daily at home but also attended the physiotherapy department at least once every two weeks. Several patients elected voluntarily to attend for supervised training twice weekly.

Results

The investigation was conducted on a total of 24 patients, 12 in the control group, and 12 in the test group. Their relevant anthropometric and clinical details are given in Table 1a and b. The 12 control subjects had a mean age of 39·7 years (SEM ±5·6) and a mean body weight of 66·3 kg (SEM ±3·5). Eight of the control subjects had aortic valve disease and four had mitral valve disease. The causes of valve lesion were rheumatic in six patients, congenital in four patients, and calcific aortic disease in the remaining two patients. The 12 subjects in the test group had a mean age of 39·7 years (SEM ±3·9) and a mean body weight of 63·2 kg (SEM ±1·9). Seven of the test subjects had aortic valve disease and five mitral valve disease. The causes of valve lesion were rheumatic in nine patients, congenital in two patients, and infective endocarditis in the remaining patient. Three patients in each group (cases 9, 11, and 12 in Table 1a, and cases 19, 23, and 24 in Table 1b) were taking digoxin but the doses remained constant during the trial.

RELATION BETWEEN SUBMAXIMAL HEART RATE AND OXYGEN CONSUMPTION

The data from each exercise test in each patient were analysed to provide a regression line relating submaximal heart rate to submaximal oxygen consumption. Three regression lines were therefore obtained in each patient, corresponding to each postoperative exercise test. In the first postoperative test, however, six patients (cases 4 and 10 of the control group, and cases 19, 20, 21, and 24 of the test group) did not complete six submaximal work loads because of complaints of dizziness, dyspnoea, or pains in the legs. In case 21 of the test group there were insufficient data to establish a regression line. In the remaining five patients regression analysis was based on fewer points. For similar reasons the 12-week test was terminated prematurely in case 19 of the test group and the 24-week test in case 10 of the control group.

A statistical analysis of 65 regression lines based on six measured points disclosed correlation coefficients of between 0·95 and 0·99 ($p<0\cdot005$ or

Table 1 *Details of patients*

Case no.	*Sex*	*Age (y)*	*Wt (kg)*	*Valve lesion*	*Aetiology*	*ECG*	*Postop 0*	*Drug 3/12*	*Therapy 6/12*
(a) *Control group*									
1	M	15	49·7	AS[1]	N	SR	—	—	—
2	M	49	58·1	AS[1]	R	SR	F20	—	—
3	M	15	51·2	AS[1]	N	SR	—	—	—
4	M	62	65·0	AS[1]	N	SR	—	—	—
5	M	58	70·0	AS[1]	N	SR	—	—	—
6	M	40	72·0	AS[2]	N	SR	F20	—	—
7	M	34	86·5	AR[1]	R	SR	—	—	—
8	M	58	60·0	AR[2]	N	SR	F20	F20	—
9	F	24	73·0	MS[3]	R	AF	DO25	DO25	DO25
10	F	60	53·0	MS[1]	R	SR	F40	—	—
11	M	40	81·3	MR[1]	R	AF	F40 DO5	DO5	DO5
12	M	37	76·0	MR[1]	R	SR	F40 DO25	F40 DO25	F40 DO25
Mean		39·7	66·3						
SEM		±5·6	±3·5						
(b) *Test group*									
13	M	62	59·0	AS[1]	N	SR	F40	—	—
14	M	18	64·5	AS[1]	N	SR	—	—	—
15	M	34	69·0	AR[1]	R	SR	F20	—	—
16	M	36	79·0	AR[2]	R	SR	F40	—	—
17	M	29	65·0	AR[2]	N	SR	F20	—	—
18	F	38	62·0	AR[4]	R	SR	—	—	—
19	M	58	65·0	AR[1]	R	AF	F40 DO5	DO5	DO5
20	F	44	52·0	MS[1]	R	SR	—	—	—
21	F	42	64·0	MS[1]	R	SR	—	—	—
22	M	35	62·0	MS[1]	R	SR	F40	—	—
23	F	55	59·2	MS[1]	R	AF	F40 DO5	F40 DO5	F40 DO5
24	F	25	58·0	MR[1]	R	SR	F40 DO25	F20 DO25	F20 DO25
Mean		39·7	63·2						
SEM		±3·9	±1·9						

SR, sinus rhythm; AS, aortic stenosis; MS, mitral stenosis; [1], Björk-Shiley prothesis; [2], Lillehei-Kester prothesis; [3] homograft; [4] heterograft; AF, atrial fibrillation; AR, aortic regurgitation; MR, mitral regurgitation; F, frusemide; D, digoxin (daily oral Rx in mg); R, rheumatic activity; N, nonrheumatic activity.

$p < 0.001$) on 61 occasions. A reduced correlation was obtained on four occasions at the first postoperative test, ranging from 0·85 to 0·93 ($p < 0.05$ or $p < 0.01$). The seven analyses based on four or five measured points (see above) showed correlation coefficients of 0·97 or 0·99 ($p < 0.005$ or $p < 0.001$). Therefore all the tests performed, except the first in case 9 of the test group, provided a significant positive relation between submaximal heart rate and oxygen consumption.

Three patients in the test group developed postoperative complications necessitating clinical intervention; cases 13 and 14 presented evidence of subacute bacterial endocarditis and case 19 cardiac failure. In addition, one patient (case 23) discontinued the training programme after 12 weeks. The results obtained in these four patients will be considered individually in a separate section of the Results (see later).

CHANGES IN CARDIORESPIRATORY FITNESS AFTER OPERATION

(a) *Individual data*

In individual subjects an increase in "cardiorespiratory fitness" is indicated by a movement of the submaximal HR/$\dot{V}_{O_2}$ relation to the right while a loss of fitness is indicated by a reversal of this movement.[9]

Original data from one patient in each group are shown in Fig. 2. The two patients are well matched in terms of age, height, and weight (see Table 1a and b). Both patients had undergone a valve replacement for aortic regurgitation with a clinically satisfactory result and recovery. In both subjects the 12-week test is associated with a movement to the right of the HR/$\dot{V}_{O_2}$ relation from that obtained three weeks after operation. The patient in the test group showed a further movement to the right at the 24-week test while the control patient showed a

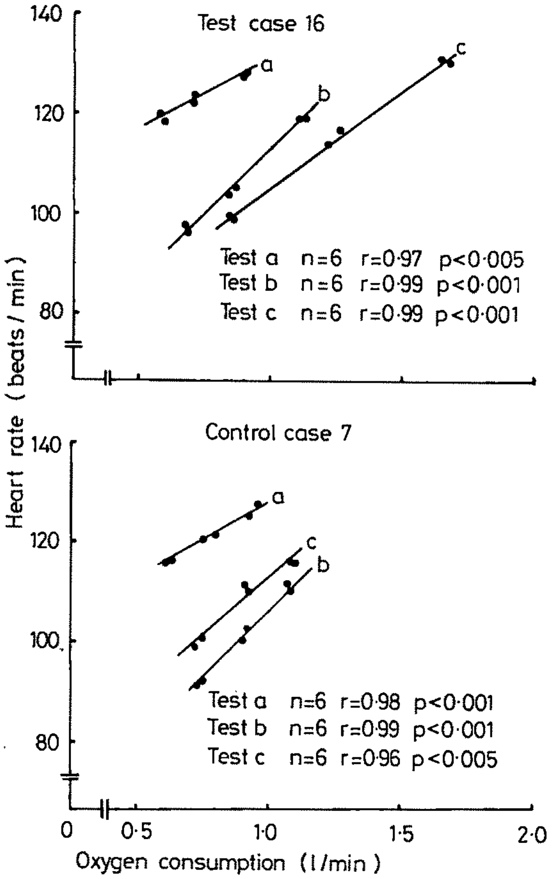

Fig. 2 *Results from test case 16, and control case 7: for each patient submaximal heart rate (beats/min) is plotted on the ordinate against submaximal oxygen consumption (l/min) on the abscissa. Measured data from exercise tests a, b, and c in each patient with the corresponding regression lines are shown. The related correlation coefficients with associated levels of significance are tabulated.*

movement to the left. This finding suggested that the training programme altered the position of the $HR/\dot{V}_{O_2}$ relation obtained at the 24-week test.

Composite plots from the remaining seven patients in the test group and the 11 patients in the control group are presented in Fig 3 and 4. In both groups the 12-week test is associated with a consistent movement of the $HR/\dot{V}_{O_2}$ relation to the right of the immediate postoperative position. In the test group, the 24-week test is associated with a further movement to the right of the $HR/\dot{V}_{O_2}$ relation from the 12-week position. In contrast, the patients in the control group show less consistent movements between the $HR/\dot{V}_{O_2}$ relations obtained at 12 and 24 weeks.

In order to establish the statistical significance of the movements of these lines, the technique described by Snedecor and Cochran was adopted.[9 12] This method compared first the slopes of the two regression lines, and second, the adjusted means to show whether the two groups of data fitted a single regression line or separate ones; that is whether the "movement" of the regression lines to the left or right was significant.

This test was used to compare the results of the 12-week and 24-week tests in each patient (Table 2). For this comparison the test group now consisted of four patients with mitral valve replacement and four patients with aortic valve replacement. The control group consisted of eight patients with aortic valve replacement and four patients with mitral valve replacement. The movement to the right of the $HR/\dot{V}_{O_2}$ relation between 12- and 24-week tests noted in each patient in the test group (Fig. 2 to 4) was confirmed as a significant difference ($p < 0{\cdot}05$). There were also significant but less consistent alterations in slope. In the control group significant alterations in slope and movements of the regression lines were also found but inspection of Fig. 2 and 3 indicates that these differences were random rather than systematic. These differences within the control group may relate to the type of valve replacement, lesion, and aetiology. In contrast, there

Table 2 *Comparison of submaximal heart rate/oxygen consumption regression lines obtained at 12 weeks and 24 weeks*

Case No.	*Control group*		*Case No.*	*Test group*	
1	Slope	NS	13	*Slope	NS
	Elevation	< 0·05		*Elevation	< 0·01
2	Slope	< 0·01	14	*Slope	NS
	Elevation	NS		*Elevation	< 0·01
3	Slope	< 0·05	15	Slope	NS
	Elevation	NS		Elevation	< 0·01
4	Slope	NS	16	Slope	< 0·01
	Elevation	< 0·05		Elevation	< 0·01
5	Slope	NS	17	Slope	NS
	Elevation	< 0·01		Elevation	< 0·01
6	Slope	NS	18	Slope	NS
	Elevation	NS		Elevation	< 0·05
7	Slope	NS	19	*Slope	NS
	Elevation	< 0·01		*Elevation	< 0·01
8	Slope	NS	20	Slope	NS
	Elevation	< 0·01		Elevation	< 0·01
9	Slope	NS	21	Slope	NS
	Elevation	< 0·01		Elevation	< 0·01
10	Slope	NS	22	Slope	< 0·01
	Elevation	< 0·01		Elevation	< 0·01
11	Slope	< 0·05	23	*Slope	NS
	Elevation	NS		*Elevation	< 0·05
12	Slope	NS	24	Slope	NS
	Elevation	< 0·01		Elevation	< 0·01

*Excluded from group comparison.

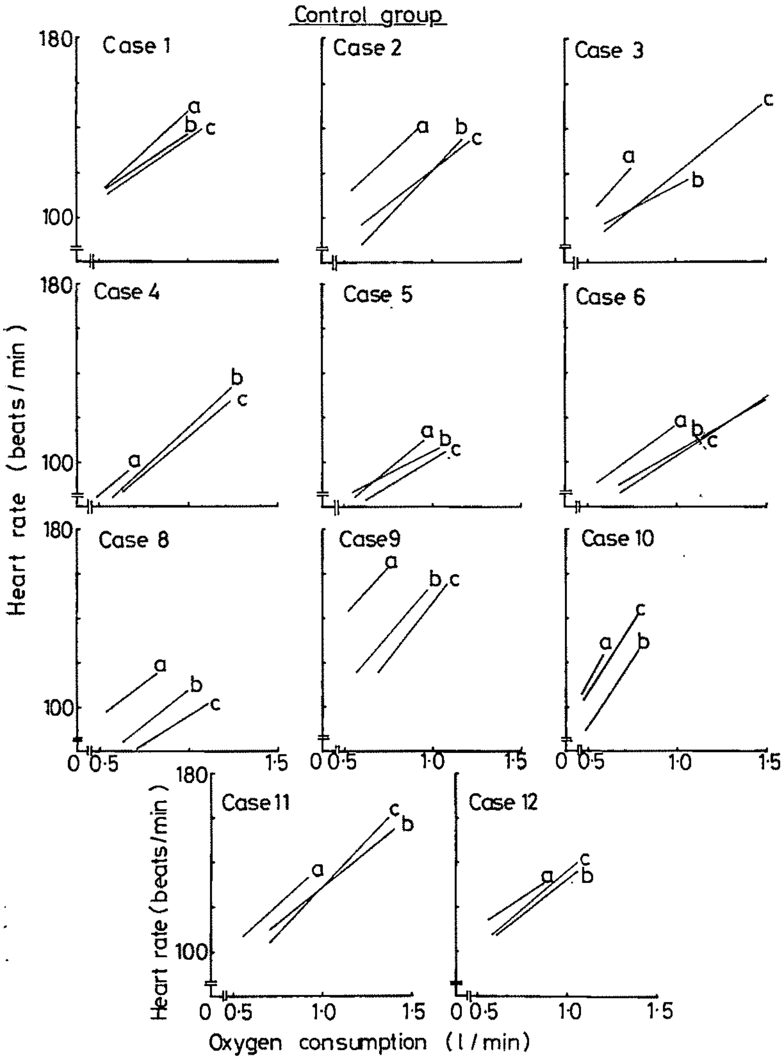

Fig. 3 *Results from 11 patients in the control group: submaximal heart rate (beats/min) is plotted on the ordinate against submaximal oxygen consumption (litre/min) on the abscissa for each patient. Regression lines calculated from the results of exercise tests a, b, and c are shown.*

was a consistent and significant movement of these regression lines to the right in the test group despite individual differences in these variables. It was therefore of interest to compare the progress of patients with rheumatic and non-rheumatic valve lesions within the control group. There were six patients with rheumatic heart disease and six patients with non-rheumatic heart disease and the exercise test appeared capable of discriminating the progress of these two subgroups. The HR/$\dot{V}_{O_2}$ regression line showed a significant movement to the right between the 12- and 24-week tests in only one of six patients with rheumatic heart disease. In contrast this movement was observed in four of the six patients in the control group who did not have rheumatic heart disease.

It was concluded that the 5BX/XBX training programme was associated with a consistent improvement in "cardiorespiratory fitness". This was defined in individual patients of the test group by a significant movement to the right of the HR/$\dot{V}_{O_2}$ regression line, between the 12- and 24-week tests. This result is similar to that demonstrated in normal subjects.[9]

(b) *Group analysis of data*

To examine *group* differences in the alteration of cardiorespiratory fitness after operation it was

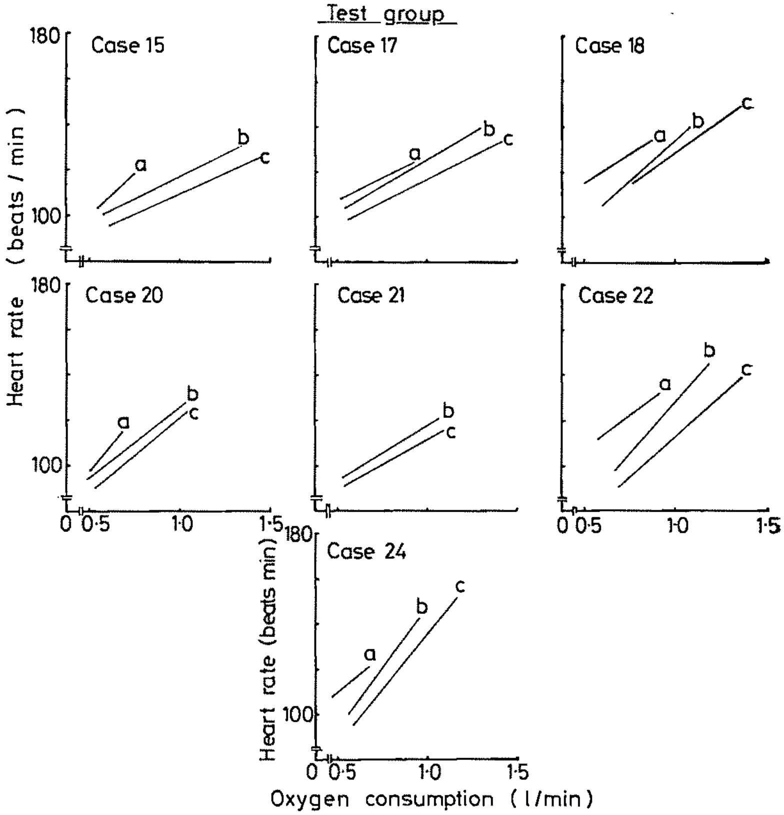

Fig. 4 *Results from seven patients in the test group: submaximal heart rate (beats/min) is plotted on the ordinate against submaximal oxygen consumption (l/min) on the abscissa for each patient. Regression lines calculated from the results of exercise tests a, b, and c are shown.*

necessary to compare the complete data for each group. Three HR/$\dot{V}_{O_2}$ regression lines were calculated from the pooled data for each of these tests in each group. The pooled HR/$\dot{V}_{O_2}$ relation from the first postoperative test was not statistically significant in either group, a finding which reflected the narrow range of heart rates obtained in these tests. This proposition is supported by the observation that the HR/$\dot{V}_{O_2}$ relation in *individual* patients was significant. The pooled HR/$\dot{V}_{O_2}$ relation from the second and third postoperative tests are illustrated in Fig. 5. The pooled data from the 12-week test yielded a significant HR/$\dot{V}_{O_2}$ relation in both groups. The positions of the regression lines did not differ significantly from each other ($p > 0{\cdot}05$). The pooled data from the 24-week test also yielded a significant HR/$\dot{V}_{O_2}$ relation in both groups. The regression line obtained in the control group, however, did not show a significant movement to the right from the 12-week position, whereas the line obtained in the test group did ($p < 0{\cdot}05$). It was concluded that the 5BX/XBX training programme had modified the postoperative recovery of cardiorespiratory fitness in patients of the test group.

No attempt was made to determine the effort tolerance of patients. All patients, however, showed an improved subjective tolerance of the higher work loads, imposed at the 12-week test. At 24 weeks further subjective improvement was more evident in the test group. This is reflected in the consistently higher loads and thus higher levels of steady state oxygen consumption achieved (cf Fig. 3 and 4).

(c) *Results of patients excluded from trial*

Four patients were excluded, three on clinical evidence, and one who failed to continue. Individual data from these four patients, together with the fitted HR/$\dot{V}_{O_2}$ regression lines are presented in Fig. 6. The results from the statistical comparison of these regression lines at 12 and 24 weeks are summarised in Table 2.

Results of sequential postoperative exercise tests in these patients will be related to their individual clinical history during the same period.

CASE 13

This 62-year-old man entered the test group after

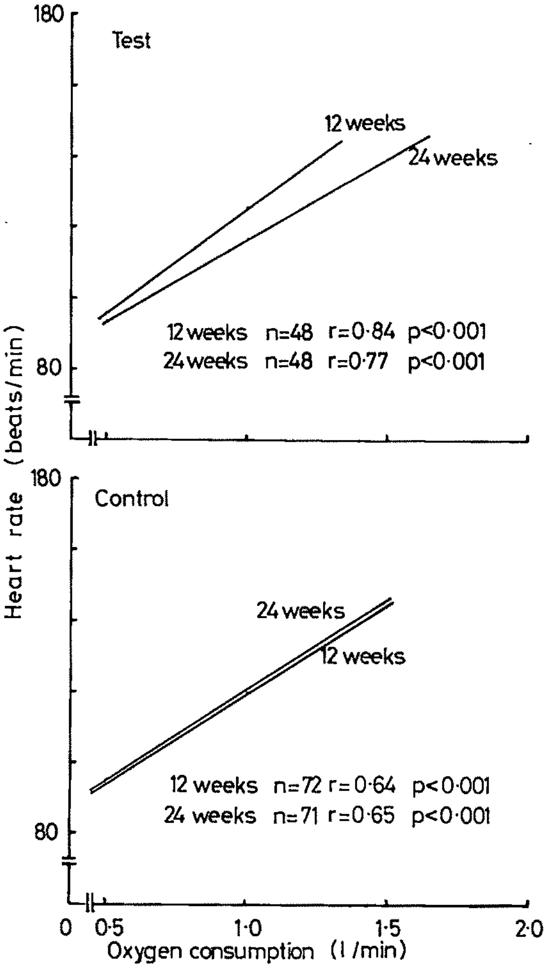

Fig. 5 *Group results for test and control patients: submaximal heart rate (beats/min) is plotted on the ordinate against submaximal oxygen consumption (l/min) on the abscissa for each group. Regression lines calculated from the pooled results of the exercise tests performed 12 and 24 weeks after operation (tests b, c) are shown for each group. The related correlation coefficients with associated levels of significance are tabulated.*

correction of isolated aortic stenosis by aortic valve replacement. This patient made steady progress through the exercise programme over the first nine weeks. Progress then slowed, and finally halted, and was associated with a complaint of lack of energy. In the twelfth week the patient complained of tiredness and night sweats. Exercise test data at 12 weeks (line b) yielded a regression line differing little in position from that obtained immediately after operation (line a). This finding contrasts with other results in both test and control groups (Fig. 3 and 4). Treatment was instituted for subacute bacterial endocarditis. Though this patient did not start training, the regression line obtained at 24 weeks (line c) again shows a "movement" to the right; commensurate with the results of other patients in the control group.

CASE 14

Preoperatively this 18-year-old man was asymptomatic. He entered the test group after aortic valve replacement to correct residual congenital aortic stenosis (a valvotomy had been performed when this patient was 5 years old). During the first 12 weeks he made rapid progress through the exercise programme. The regression line from the 12 week test (line b) showed pronounced movement to the right from the postoperative position (line a). Progress with training, however, then slowed. At the twenty-first postoperative week the patient complained of a persistent "flu like" illness and felt too tired to continue the exercise programme. The test at 24 weeks resulted in a regression line (line c), displaced to the left of that at 12 weeks (line b), despite some training during this period. Subacute bacterial endocarditis was later diagnosed and treated. An additional exercise test performed at 30 weeks resulted in a regression line (line d) showing a movement to the right from the 24-week position.

CASE 19

This 58-year-old man entered the trial after correction of aortic regurgitation by aortic valve replacement. After 10 weeks of training he was unable to complete the exercise sequences within the required time and exercise was associated with worsening dyspnoea and a pronounced tachycardia. He complained of feeling "worse off" than before the operation. Clinical examination confirmed a diagnosis of progressive cardiac failure. The exercise test performed at 12 weeks resulted in a regression line (line b) lying to the left of the immediate postoperative line (line a). After treatment, and on long-term diuretic therapy, this patient undertook a further exercise test at 24 weeks. This test resulted in a regression line with a position well to the right of the previous two tests.

CASE 23

This 55-year-old woman underwent mitral valve replacement for the correction of mitral stenosis. Domestic circumstances prevented her from continuing the exercise programme after 12 weeks. The test at 12 weeks resulted in a regression line (line b) lying to the right of the position after

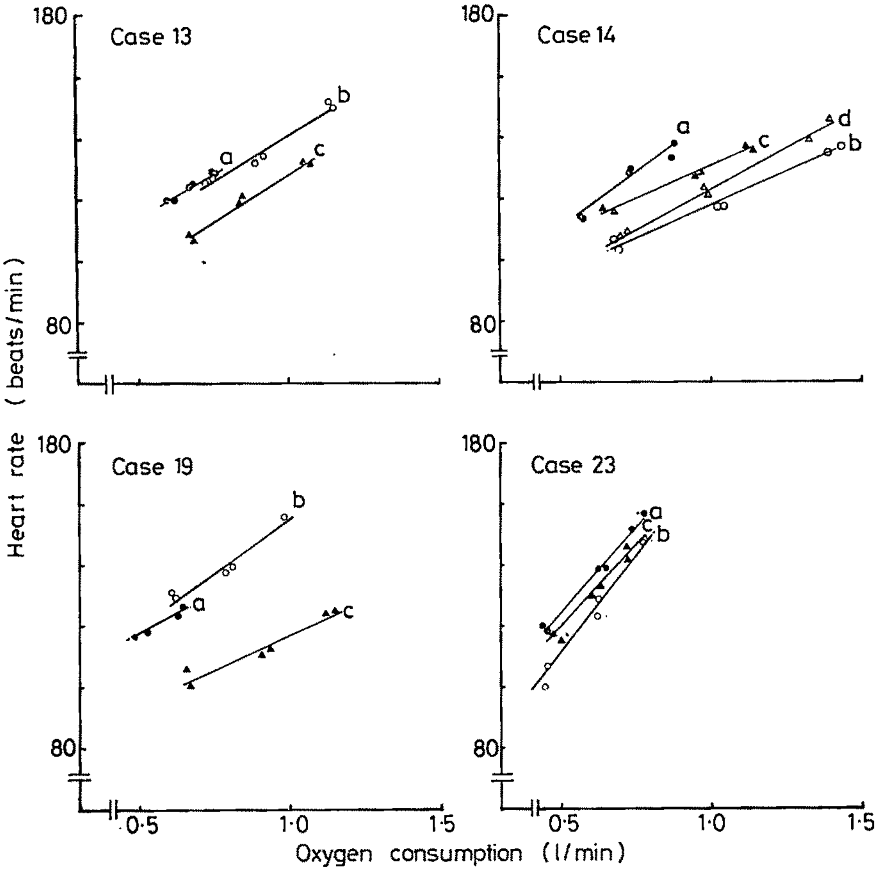

Fig. 6 *Results from patients excluded from the test group: submaximal heart rate (beats/min) is plotted on the ordinate against submaximal oxygen consumption (l/min) on the abscissa for each patient. Measured data from exercise tests a, b, and c (also d in case 14—see text) with the corresponding regression lines are shown.*

operation. However, the line from the exercise test at 24 weeks (line c), after discontinuing training, was to the left of the 12 week position, a finding previously noted in patients of the control group (Fig. 3).

Cases 13, 14, and 19 were unable to maintain steady progress through the training programme. This undoubtedly drew attention to a deteriorating clinical condition which was confirmed on formal exercise testing. Interpretation of these results necessitated additional clinical information but their development appeared to predate the appearance of unequivocal clinical signs.

Discussion

This study attempted to provide objective evidence of a change in cardiorespiratory fitness when patients recovering from surgery for valvular heart disease undertook a programme of physical training. Only a small number of patients was studied, due mainly to strict criteria governing entry to the trial. For logistic reasons conventional randomisation between test and control groups was not possible. An allocation solely based on domicile, however, did not result in any other relevant differences in the composition of the two groups.

For this study a valid index of cardiorespiratory fitness and an acceptable training programme were required. In addition, sequential exercise tests provided an early indication of postoperative complications in three patients. The application of exercise tests in the routine follow-up of postoperative cardiac patients will therefore be examined.

VALID INDEX OF CARDIORESPIRATORY FITNESS

An index was required to show an "improvement" or deterioration in the cardiorespiratory fitness of individual patients. Validation therefore demanded the demonstration of systemic alterations in this index, with interventions designed to alter cardiorespiratory fitness (for example periods of training or detraining). This index will not provide an absolute measure of fitness but will follow *changes* in individual patients provided its reproducibility is acceptable. Maximal oxygen consumption ($\dot{V}_{O_2}$ max) is conceptually attractive to fulfil this role, since alterations in this value with training and detraining have been repeatedly shown in normal individuals, at least on the basis of a change in *group* mean values. Several points, however, must be considered before measurement of $\dot{V}_{O_2}$ max is made in a clinical population. This measurement must be divorced from any subjective considerations. The objective criteria used to define a measurement "endpoint" demand a lengthy and exhausting procedure.[13] Furthermore, the reproducibility of this measurement within a normal sedentary population is ill defined.[9] As a result, it was considered unrealistic and potentially hazardous to ask cardiac patients to adhere to a test procedure developed in well trained and motivated subjects. Adopting a "symptom limited" measurement of $\dot{V}_{O_2}$ max[14 15] was inappropriate because these methods introduce a subjective endpoint whose reproducibility cannot be adequately examined.

An index based on submaximal exercise data was therefore necessary. Since the submaximal HR/$\dot{V}_{O_2}$ relation is constructed from relatively simple measurements and its linearity permits the application of conventional statistical techniques, it has formed the basis of several such indices. Both the slope of this relation and heart rates interpolated at a fixed submaximal oxygen consumption have been incorporated into separate indices of cardiorespirafitness.[16 17] Neither index, however, had been validated in the terms required by this study. Furthermore, neither is a complete description of a relation which may alter in both slope and elevation.[16] An earlier investigation[9] showed this relation to be a valid index of cardiorespiratory fitness provided account was taken of the complete data relating to individual regression lines. The results of a single exercise test were also found to form an adequate baseline from which to follow alterations in cardiorespiratory fitness.

This index was therefore selected to follow sequential alterations from a postoperative baseline. This baseline reflected the combined effects of preoperative limitation of activity, surgical intervention, and postoperative immobilisation. It was not possible to state that individual patients showed an equal deterioration of cardiorespiratory fitness at this time; only that *changes* within a given patient would be detected. In addition, it was not possible to predict the nature of the mechanism responsible for these changes. It is of interest, however, that most of the patients with rheumatic heart disease and with mitral valve replacement in the control group failed to show a detectable improvement using this index. In contrast, most of the remaining patients with non-rheumatic heart disease continued to improve in the postoperative period. That recovery in the rheumatic heart is less satisfactory than that in the non-rheumatic heart has been documented in previous investigations using catheter studies and changes in cardiac output relative to oxygen consumption at rest and exercise[5 6]

ACCEPTABLE TRAINING PROGRAMME

A training programme for cardiac patients should allow individual prescription, be gently graded, safe, and cause minimal interference with normal daily routine. The 5BX/XBX exercise programme satisfied these criteria in normal subjects[9] and in patients with angina pectoris.[18] No complications attributable to training arose in the eight patients who undertook the complete training procedure. Several patients approached closely to the age related "goal level" of this programme but none actually achieved it. This may reflect an initial low level of fitness or an inability to attain targets predicted from normal individuals. The post-exercise heart rate after a training session (recorded over the first 20 s after exercise) was between 130 and 160 beats/min. Individual recovery heart rates first became higher and then consistent as training progressed. This finding illustrates the carefully graded nature of the exercise sequences.

Twelve weeks after the first postoperative exercise test the HR/$\dot{V}_{O_2}$ relation moved to the right in the control group, indicating an improvement in "cardiorespiratory fitness". This trend, however, was not maintained over the next 12 weeks, especially in patients with rheumatic heart disease involving the mitral valves. In contrast, patients in the test group, in the majority of whom the cause of either the aortic or mitral valve lesions was rheumatic heart disease, showed an additional improvement in cardiorespiratory fitness over the same period. This finding is consistent with the hypothesis that the 5BX/XBX programme improved the cardiorespiratory fitness of patients in the test group and this occurred against a background of "spontaneous" improvement in both groups over the first 12 weeks. Most patients with rheumatic heart disease and with mitral valve replacement who did not participate in the training programme failed to maintain this improvement.

Therefore, successful insertion of a prosthetic valve did not result in sustained improvement in cardiorespiratory fitness 12 weeks after surgery but this was endowed by a suitable physical training programme. The improvement in the test group was reflected in a reported increase in normal daily activity compared with control patients. It is not known, however, whether this improvement will be maintained when regular physical training is withdrawn 24 weeks after operation.

SEQUENTIAL POSTOPERATIVE EXERCISE TESTS

A progressive limitation of exercise tolerance is a common presenting symptom of adult valvular heart disease. Functional disability is commonly graded in these terms, to lend a degree of "objectivity" to the assessment of individual patients (for example the widely used New York Heart Association classification).[19] Assessment by means of a formal exercise test is therefore a logical development,[20 21] particularly as discrepancies have been shown between the subjective account of symptoms and the results of exercise tests.[22] This approach has not been generally adopted, however, except as an adjunct to catheter studies. Similarly, pre- and postoperative exercise tests, to adjudge the efficacy of surgical intervention, have not been developed, though several recommendations have been made to this effect.[22 23]

The results of the present study emphasise the individual pattern of recovery observed after cardiac surgery. The timing of a sequence of postoperative exercise tests would therefore require careful consideration. A major reason patients gave for consenting to enter this trial was that an exercise test would help them find out "what I can do". This suggested that sequential postoperative exercise tests might play a useful role in the follow-up and counselling of these patients. The results in patients who developed postoperative complications supported this approach, though they were essentially anecdotal observations. A formal trial of exercise tests used in this manner, however, would indicate their value.

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References

1 Working Party on Cardiac Rehabilitation. *J R Coll Physicians Lond* 1975; **9:** 281–346.

2 Bassey EJ, Bennett T, Birmingham AT, Fentem PH, Fitton D, Goldsmith R. Effects of surgical operation and bed rest on cardiovascular responses to exercise in hospital patients. *Cardiovasc Res* 1973; **7:** 588–92.

3 Carswell S. Changes in aerobic power in patients undergoing elective surgery. *J Physiol (Lond)* 1975; **251:** 42–3P.

4 Andersen A, Hillestad L, Rasmusson K, Myhre E. The cardiac response to exercise in aortic valvular disease before and after ball valve replacement. *Acta Med Scand* 1971; **190:** 251–5.

5 Bristow JD, Kremkau EL. Haemodynamic changes after valve replacement with Starr-Edwards prostheses. *Am J Cardiol* 1975; **35:** 716–24.

6 Hildner FJ, Javier RP, Cohen LS, *et al.* Myocardial dysfunction associated with valvular heart disease. *Am J Cardiol* 1972; **30:** 319–26.

7 Morgan JJ. Hemodynamics one year following mitral valve replacement. *Am J Cardiol* 1967; **19:** 189–95.

8 Björk VO, Böök K, Cernigliaro C, Holmgren A. The Björk-Shiley tilting disc valve in isolated mitral lesions. *Scand J Thorac Cardiovasc Surg* 1973; **7:** 131–48.

9 Kappagoda CT, Linden RJ, Newell JP. Effect of the Canadian Air Force training programme on a submaximal exercise test. *Q J Exp Physiol* 1979; **64:** 185–204.

10 Kappagoda CT, Stoker JB, Linden RJ. A method for the continuous measurement of oxygen consumption. *J Appl Physiol* 1974; **37:** 604–7.

11 Royal Canadian Air Force. *Physical fitness.* Harmondsworth: Penguin Books, 1964.

12 Snedecor GW, Cochran WG. *Statistical methods.* 6th ed. Ames, Iowa: Iowa State University Press, 1967: 432–6.

13 Åstrand PO. Quantification of exercise capability and evaluation of physical capacity in man. *Progr Cardiovasc Dis* 1976; **19:** 51–67.

14 Gilbert R, Auchincloss JH Jr. Cardiac and pulmonary function at the exercise breaking point in cardiac patients. *Am J Med Sci* 1979; **257:** 370–81.

15 Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. *Am J Cardiol* 1973; **30:** 757–62.

16 Cotes JE. Rational exercise testing: the case for simple indices of submaximal exercise: ventilation, tidal volume and cardiac frequency. *Scand J Respir Dis* 1971; **77,** suppl: 223–7.

17 Spiro SG, Juniper E, Bowman P, Edwards RHT. An increasing work rate test for assessing the physiological strain of submaximal exercise. *Clin Sci Mol Med* 1974; **46:** 191–206.

18 Raffo JA, Luksic IY, Kappagoda CT, Mary DASG, Whitaker W, Linden RJ. Effects of physical training on myocardial ischaemia in patients with coronary artery disease. *Br Heart J* 1980; **43:** 262–9.

19 New York Heart Association. *Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels.* 5th ed. Boston: Little Brown, 1953; 112.

20 Nylin G. More recent developments of heart function tests. *JAMA* 1937; **109:** 1333–7.

21 Wyndham CG, Ward JS. An assessment of the exercise capacity of cardiac patients. *Circulation* 1957; **16:** 384–93.

22 Bergy GG, Bruce RA. Discrepancies between subjective and objective responses to mitral commissurotomy. *N Engl J Med* 1955; **253:** 887–91.

23 Gilmour DG, Spiro SG, Raphael MJ, Freedman S. Exercise tests before and after heart valve replacement. *Br J Dis Chest* 1976; **70:** 185–94.

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Br Heart J 1980; **44:** 650–6

Assessment of chest pain in hypertrophic cardiomyopathy using exercise thallium-201 myocardial scintigraphy

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SUMMARY Exercise thallium-201 myocardial scintigraphy was performed in 23 patients with hypertrophic cardiomyopathy. Eighteen patients presented with chest pain which was a persistent symptom in 11. Selective coronary arteriography was performed in 16 patients and showed normal coronary arteries in 15 and insignificant luminal irregularities in one patient.

Eighteen patients had abnormal scintigrams. Three had an abnormal distribution of tracer entirely attributable to asymmetric septal hypertrophy, whereas 15 had discrete tracer uptake defects which could not be explained solely by myocardial hypertrophy. In this latter group of patients three scintigraphic patterns were identified: (1) in 10 patients defects were seen in scintigrams immediately after exercise but not in delayed images obtained four to six hours later. Eight of these patients had chest pain. (2) Four patients had uptake defects seen in both initial and delayed images. One patient had chest pain. (3) In three patients, one of whom had chest pain, tracer defects were seen only in delayed images and were not apparent in the initial scintigrams.

Chest pain occurred in eight out of 10 patients with scintigraphic evidence of myocardial ischaemia but was present in only three out of 13 patients with non-ischaemic scintigrams.

The value of exercise thallium-201 myocardial imaging as a diagnostic technique in hypertrophic cardiomyopathy appears limited. Scintigraphic evidence of regional myocardial ischaemia in the absence of significant coronary artery disease, however, contributes to an understanding of the mechanism of angina production in patients with hypertrophic cardiomyopathy.

Despite angiographically normal or dilated coronary arteries, anginal chest pain is a dominant symptom in many patients with hypertrophic cardiomyopathy.[1] Exercise thallium-201 (^{201}Tl) myocardial scintigraphy has been shown to be a sensitive technique for detecting abnormalities of regional myocardial perfusion in patients with angina pectoris caused by coronary artery disease.[2 3] This technique has also been used for the detection of asymmetric septal hypertrophy in patients with hypertrophic cardiomyopathy.[4] Chest pain in hypertrophic cardiomyopathy, however, has not been studied previously using myocardial scintigraphy. In this communication we report the findings on thallium-201 myocardial scintigraphy in patients with hypertrophic cardiomypathy, and their relation to chest pain.

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Patients and methods

Twenty-three patients (17 male, six female, aged 26 to 68 years) with hypertrophic cardiomyopathy were studied. Eighteen patients presented with angina pectoris, which was a persisting symptom at the time of investigation in 11. All patients had a full clinical examination, resting 12-lead electrocardiogram, and chest *x*-ray. No patient had hypertension or aortic valve disease. The diagnosis of hypertrophic cardiomyopathy was established by echocardiography and contrast left ventriculography.

Echocardiography showed asymmetric septal hypertrophy (septal to posterior wall ratio greater than 1·3) in 22 patients. Echocardiographic evidence of left ventricular outflow obstruction (mitral systolic anterior motion and/or premature aortic valve closure) was present in 11. One patient had echocardiographic evidence of concentric left ventricular hypertrophy in the presence of a family history of hypertrophic cardiomyopathy and a diagnostic angiographic appearance.

At cardiac catheterisation a left ventricular intracavity pressure gradient was detected in 10 patients at rest and in a further three after isoprenaline stimulation. Ten patients had no resting gradient and did not receive isoprenaline.

Contrast left ventricular angiography showed systolic obliteration of the ventricular cavity in 14 patients. Varying degrees of septal and papillary muscle hypertrophy were seen in all 23 patients. Mild mitral regurgitation was present in seven patients and a moderate degree in one. In 15 patients normally patent coronary arteries were demonstrated by selective arteriography. One patient had minor coronary luminal irregularities which were not considered significant. Seven patients without persistent chest pain did not have selective coronary arteriography.

MYOCARDIAL IMAGING

All patients underwent a graded maximal exercise test on a bicycle ergometer with continuous monitoring of the electrocardiogram using a single electrode in the V5 position. 1·5 mCi ^{201}Tl was given intravenously at the limiting end-point of exercise (which was angina pectoris in five patients) and submaximal exercise was continued for two minutes.

Myocardial imaging was performed with a standard field of view gamma camera (Ohio Nuclear Series 100 or 120) equipped with a high sensitivity, parallel-hole collimator. Immediately after exercise myocardial images were obtained routinely in all patients in four standard projections (anterior, left anterior oblique 45° and 55°, and left lateral) and further myocardial images were acquired in selected views four to six hours after the initial administration of tracer. 200 000 counts were recorded in each projection. The images were digitised and stored for later retrieval using a dedicated minicomputer (Digital Equipment Corporation, Gamma 11). A 50 per cent background erase and interpolation was applied routinely to all images.

Images were displayed on a television monitor in 16 grades of colour, linearly related to count density. Analysis was performed by two independent observers. The images were classified as normal if the distribution of tracer was homogeneous and if the outline of left ventricular myocardial tracer activity appeared of normal shape and symmetry. In addition to any observed abnormalities of shape or symmetry, regions of relatively

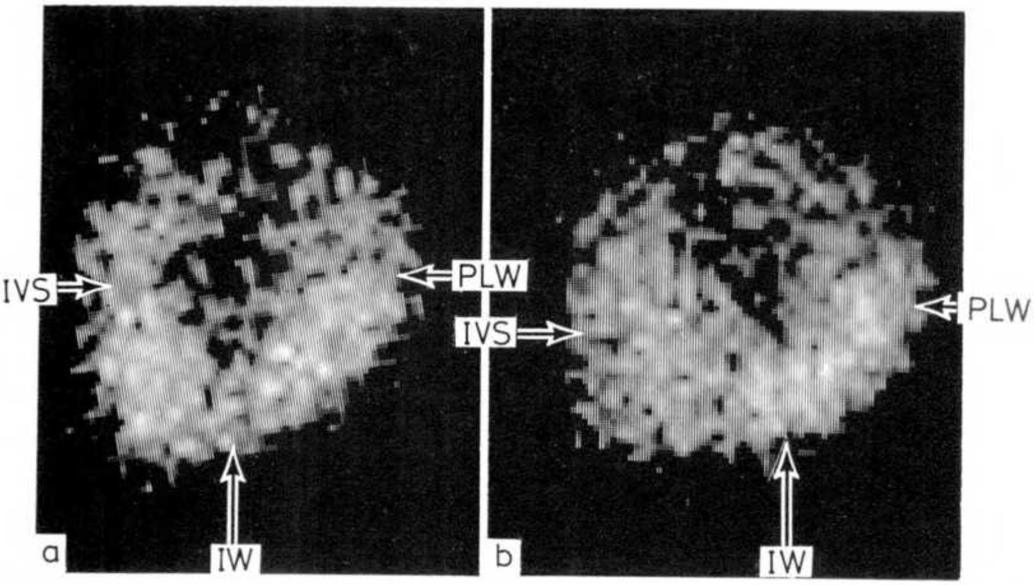

Fig. 1 *LAO 45° scintigrams from (a) a normal subject and (b) a patient with hypertrophic cardiomyopathy. The increased width of septal tracer activity and abnormal image shape in (b) are attributable to asymmetric septal hypertrophy. IVS, interventricular septum; IW, inferior wall; PLW, posterolateral wall.*

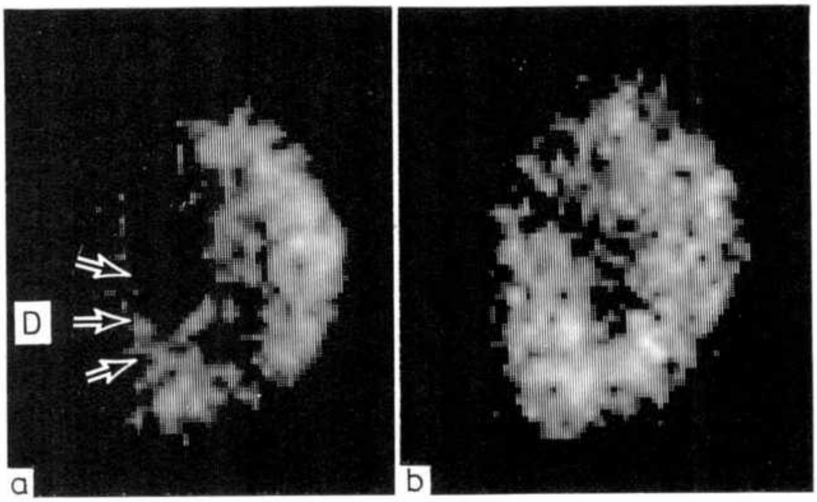

Fig. 2 *LAO 45° scintigrams from a patient with hypertrophic cardiomyopathy and normal coronary arteries (a) immediately after tracer administration during peak exertion and (b) four hours later. A defect of tracer uptake (D) is seen in the septum in (a). Redistribution of thallium to this region seen in the delayed image suggests that the defect was the result of regional myocardial ischaemia.*

diminished tracer activity were identified and classified according to their site (septal, apical, inferior, anterolateral, or posterolateral).

The prevalence of each of four symptoms (angina, dyspnoea, palpitation, and syncope) was compared with the observed scintigraphic patterns. Fisher's exact test was used to assess the statistical significance of the results.

Results

SCINTIGRAPHIC APPEARANCES

A normal intramyocardial distribution of tracer was seen in five patients, one of whom had chest pain. Abnormal myocardial scintigrams were found in 18 patients. Three patients did not have uptake defects though the septum was clearly thicker than the posterolateral wall in the LAO projection (Fig. 1). Discrete tracer uptake defects not attributable to abnormal anatomy alone were found in the remaining patients and could be classified into three types: (1) the initial images of 10 patients (group 1) showed discrete areas of diminished tracer accumulation which later became normal in delayed scintigrams (Fig. 2): eight of these patients had chest pain; (2) in four patients (group 2) tracer defects were present in the initial scintigrams and persisted in delayed images and were therefore regarded as fixed defects (Fig. 3): one of these patients had chest pain; (3) finally in three patients, one of whom had chest pain, septal tracer defects appeared in the delayed images which had not been present in the initial scintigrams (Fig. 4). The distribution of the observed defects is shown in the Table.

PREVALENCE OF SYMPTOMS

The prevalence of anginal chest pain was significantly greater ($p < 0{\cdot}01$) in patients in group 1 than in the remainder of the patients studied (Fig. 5). The prevalence of other symptoms (dyspnoea, palpitation, and syncope) was not significantly greater in any of the groups of patients described.

COMPARISON WITH ELECTROCARDIOGRAMS

There was no significant difference in the prevalence of voltage criteria for left ventricular hypertrophy between any of the groups of patients. Abnormal Q waves were present in 10 patients. Five of these had septal tracer defects (groups 1 or 2) and inferior or inferolateral Q waves. Of the other five, three had no tracer defects, one had an apical defect, and one a septal tracer defect in the delayed images only (group 3).

When the distribution of resting ST segment and T wave abnormalities was compared with that of tracer defects 15 out of 19 defects in groups 1 and 2 had corresponding ST/T abnormalities. The three patients in group 3 (reduced septal tracer

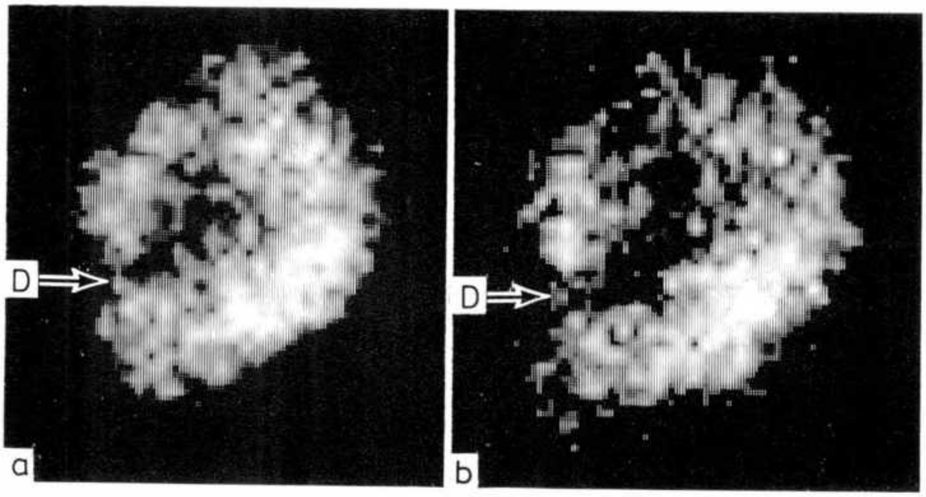

Fig. 3 *LAO 45° scintigrams from a patient with hypertrophic cardiomyopathy (a) immediately after tracer administration and (b) four hours later. The defect in tracer uptake (D) in the lower septum in (a) is seen as a persistent abnormality in (b).*

activity on delayed images only) had no corresponding septal ST-T changes but showed such changes in the inferior and lateral leads. Resting ST-T abnormalities occurred in regions without tracer defects in 17 patients including eight with no defects on their scintigrams.

Only two patients showed at least 2 mm ST segment depression in lead V5 during exercise. One had the severe septal defect shown in Fig. 2 and the other a fixed septal tracer defect.

COMPARISON WITH ECHOCARDIOGRAMS AND CATHETER FINDINGS

Septal thickness and septal/posterior wall ratio

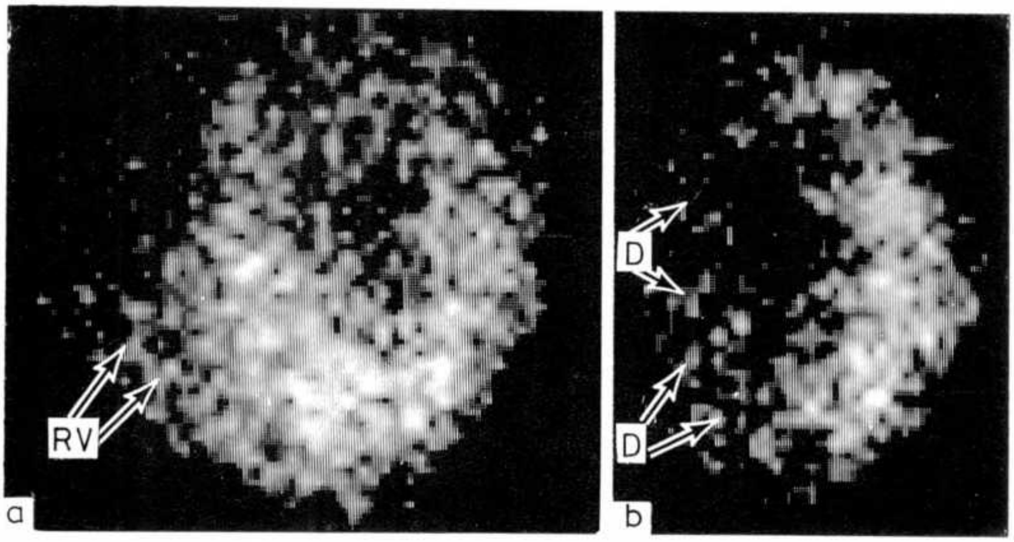

Fig. 4 *LAO 45° scintigrams in another patient with hypertrophic cardiomyopathy (a) immediately and (b) four hours after tracer administration. No tracer uptake defect is visible in (a), but diminished tracer activity (D) in the septum is seen in the delayed image. There is also increased uptake of tracer by the right ventricular myocardium (RV) in this patient.*

measured from the echocardiogram were compared in the groups of patients with the different scintigraphic patterns described. There was no significant difference in these measurements among the various groups, and in particular no significant difference was seen when group 1 was compared with the remainder.

Echocardiographic evidence of left ventricular outflow obstruction occurred in six patients from group 1 and in five other patients. Similarly there was no significant difference between group 1 and the remainder when left ventricular intracavity gradients and left ventricular end-diastolic pressure recorded at cardiac catheterisation were examined.

Estimation of septal and posterolateral wall thickness from the left anterior oblique 45° scintigrams was prevented by tracer deficits in the region in half of the patients. In the remainder the lack of edge definition prevented accurate or consistent measurements.

Discussion

Myocardial imaging using ^{201}Tl may be used to detect regional myocardial ischaemia caused by coronary artery disease.[2 3] Uptake of this tracer by myocardial cells in any region is dependent largely on coronary blood flow at the time of tracer administration.[5] During exercise coronary flow increases, unless restricted, for example, by a proximal coronary artery stenosis. Thus, when ^{201}Tl is given during exercise its delivery to myocardium beyond such a stenosis is restricted, while delivery to unaffected regions is increased. Furthermore, increased oxygen demand during exercise may lead to myocardial hypoxia distal to the stenosis. Since ^{201}Tl uptake into myocardial cells is by active, ATP-dependent transport requiring oxygen, tracer uptake is impaired by hypoxia, which further enhances the relative paucity of tracer accumulation in the ischaemic zone. This is seen as an area of relatively diminished tracer activity on myocardial images acquired immediately after ^{201}Tl administration during exercise. Over the next few hours the isotope is redistributed, both to previously ischaemic myocardium and to extracardiac organs. Repeat imaging several hours after tracer administration allows differentiation of transiently ischaemic myocardium from a region of previous infarction[6] which will not show accumulation of tracer activity in delayed images.

In hypertrophic cardiomyopathy additional factors are encountered which may affect scintigraphic appearances. Septal thickness is increased and may be seen as a wider band of tracer activity when seen in profile. Septal motion, however, is reduced and posterior wall motion often increased.

Table *Types and distribution of tracer defects seen in 15 patients*

Observed abnormality	*No. of patients*	*No. of distinct defects*			
		Septal	*Apical*	*Inferior*	*Total*
Ischaemic defects seen on initial but not on delayed images	10	8	4	2	14
Fixed defects seen on both initial and delayed images	4	3	1	0	4
Late defects seen only on delayed images	3	3	0	0	3

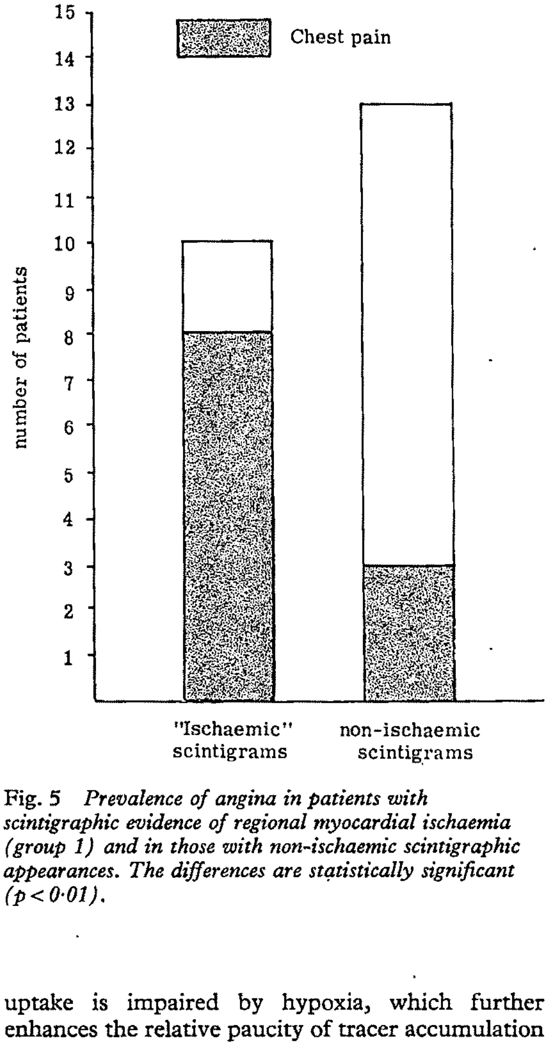

Fig. 5 *Prevalence of angina in patients with scintigraphic evidence of regional myocardial ischaemia (group 1) and in those with non-ischaemic scintigraphic appearances. The differences are statistically significant* ($p<0·01$).

Since ^{201}Tl scintigrams integrate both systolic and diastolic events the profiled image of the septum will appear relatively thinner, and that of the posterolateral wall relatively wider as a result of these differences in wall motion. Tracer activity in hypertrophied papillary muscles and systolic cavity obliteration may increase apparent wall thickness near the apex. These factors may contribute to an increased apparent septal thickness near the apex, reported by Bulkley *et al.*[4] in hypertrophic cardiomyopathy. We consider myocardial scintigraphy to be an inappropriate technique for the measurement of wall thickness, both because of its low resolution and because of the tracer defects seen in many of our patients.

The precise significance of some of these defects is uncertain. Defects seen on the initial images but not on delayed imaging provide evidence, however, of regional myocardial ischaemia during exercise in the absence of coronary artery disease. Anginal chest pain was significantly more common in patients with this type of defect. The distribution of these defects (Table) corresponds with the known distribution of myocardial fibre disarray and hypertrophy in hypertrophic cardiomyopathy,[7] but regional ischaemia cannot be attributed to myocardial hypertrophy alone. We found ischaemic scintigraphic defects in some of our patients, but not in others with an equal degree of hypertrophy. We suggest that regional myocardial ischaemia may occur when localised abnormalities of contraction and relaxation generate high intramyocardial pressures in both systole and diastole, and thereby reduce local coronary flow. Since the greater part of coronary flow occurs in diastole, abnormalities of left ventricular *relaxation* are probably of greatest importance in the genesis of myocardial ischaemia.[8] This is emphasised by the increased incidence of angina pectoris associated with impaired left ventricular filling in hypertrophic cardiomyopathy.[9]

Two other types of tracer defect were observed in our patients. Fixed defects, present in both initial and delayed images, probably represent areas of myocardial scarring, known to occur in hypertrophic cardiomyopathy.[10] Alternatively these defects might be the result of severe abnormalities of regional contraction and relaxation, sufficient to maintain ischaemia at rest and prevent redistribution of ^{201}Tl to a region with diminished uptake on the initial scintigrams. Septal tracer defects, however, seen in three patients in the delayed images only, cannot be attributed to septal ischaemia since there was no impairment of local ^{201}Tl uptake in the initial images. The subsequent appearance of relatively reduced tracer activity in the septum after several hours may be the result of more rapid tracer elimination from the septum than from the posterolateral wall. Since the regional clearance of ^{201}Tl from the myocardium is independent of blood flow,[11] a more rapid leakage of isotope from abnormal septal myofibrils would provide a possible explanation for this phenomenon. Alternatively changes in left ventricular geometry or wall motion may give rise to an asymmetry of tracer activity, even if the intramyocardial distribution is homogeneous. The three patients with this scintigraphic pattern had no clinical or other investigatory features to distinguish them from the remainder of the patients in the study.

Thus, our findings indicate that at least three abnormal scintigraphic patterns, not attributable to myocardial hypertrophy alone, may be found in patients with hypertrophic cardiomyopathy. In particular, scintigraphic evidence of regional myocardial ischaemia during exercise was found in several patients and offers an explanation for angina pectoris in this condition. Regional myocardial ischaemia could not be identified from the resting electrocardiograms and single lead exercise electrocardiography was a relatively insensitive indicator of ischaemia in this group of patients. Further studies are indicated to establish the clinical and in particular the prognostic significance of scintigraphic abnormalities in hypertrophic cardiomyopathy.

References

1 Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the natural history. *Circulation* 1968; **37:** 759–88.

2 Bailey IK, Griffith LSC, Rouleau J, Strauss HW, Pitt B. Thallium-201 myocardial perfusion imaging at rest and during exercise. Comparative sensitivity to electrocardiography in coronary artery disease. *Circulation* 1977; **55:** 79–87.

3 Wainwright RJ, Maisey MN, Sowton E. Segmental quantitative thallium scintigraphy in diagnosis of coronary artery disease—correlation with coronary arteriography and exercise stress testing (abstract). *Br Heart J* 1978; **40:** 447.

4 Bulkley BH, Rouleau J, Strauss HW, Pitt B. Idiopathic hypertrophic subaortic stenosis; detection by thallium-201 myocardial perfusion imaging. *N Engl J Med* 1975; **293:** 1113–6.

5 Strauss HW, Harrison K, Langan JK, Lebowitz E, Pitt B. Thallium-201 for myocardial imaging: relation of thallium-201 to regional myocardial perfusion. *Circulation* 1975; **51:** 641–5.

6 Pohost GM, Zir LM, Moore RH, McKusick KA, Guiney TE, Beller GA. Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation* 1977; **55:** 294–302.

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Morphological considerations pertaining to recognition of atrial isomerism

Consequences for sequential chamber localisation

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SUMMARY The atrial morphology and venous connections were assessed "blind" in 51 necropsy specimens from patients with visceral heterotaxy. This was compared with bronchial morphology as established by dissection. Six specimens were found to have both atria and bronchi in situs solitus or inversus, and were rejected. In the remainder, atrial isomerism was diagnosed, though this required minor revision of the atrial assessment in two patients. Thirty-four patients had isomeric right atria and bronchi, while 11 had isomeric left atria and bronchi.

In seven cases, splenic status was unknown, but in seven of the remaining 38 (18·4%) atrial isomerism was not associated with either asplenia or polysplenia. Nevertheless, right isomerism was strongly associated with total anomalous pulmonary venous drainage (as is asplenia) and left isomerism was likewise associated with interruption of the inferior vena cava (as is polysplenia). Bilateral superior venae cavae and hepatic veins, and absence of the coronary sinus, were frequent in both forms of isomerism (as they are in asplenia and polysplenia).

These findings suggest that atrial situs can be defined as solitus inversus, right isomerism, and left isomerism. This determination of atrial situs is quite independent of any other abnormalities of visceral situs. The high incidence of anomalies of both venous return and common atrium resulted in presumed complete mixing of blood at atrial level in all but one patient (97·8%), making the haemodynamic connection between atria and ventricles almost always ambiguous. To describe this anatomical connection as ambiguous when there are two ventricles present is therefore no more than a recognition of anatomical and haemodynamic reality.

Visceral heterotaxy presents two fundamental questions to the cardiac morphologist. First, are the atrial chambers of ambiguous or indeterminate morphology,[1 2] or are they isomeric? Second, if the atria are isomeric is it possible to avoid the necessity for describing the atrioventricular connection as ambiguous? In theory, it might be feasible to describe the connections as concordant or discordant on the basis of analysis of venous connections and ventricular morphology.

A further practical question for the clinician is how best to predict the presence of atrial isomerism before cardiac catheterisation. While it is well recognised that bronchial morphology correlates well with atrial morphology[3–7] and that bronchial situs can be objectively diagnosed in life,[5] isolated exceptions to this rule have been reported.[4 8 9] The real question is not whether there are any exceptions, but how frequent they are.

To investigate these questions we have studied visceral situs, atrial morphology, and venous connections in 45 patients in whom the diagnosis of visceral heterotaxy was made or confirmed at necropsy.

Subjects and methods

The case material came from the necropsy collections at The Hospital for Sick Children, Great

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Ormond Street, the Brompton Hospital, and Killingbeck Hospital, Leeds. Cases selected for study were those which did not unequivocally have situs solitus or inversus, provided that one or both lungs were attached to the heart. The mediastinum and hila of the specimens were thoroughly dissected by one of us (FJM), so as to expose the pulmonary veins, pulmonary arteries, and bronchi. Bronchial morphology was assessed by noting the course of the central pulmonary artery as it continued, travelling posteriorly and inferiorly, into the lower lobe pulmonary artery. If this arterial pathway passed between two bronchi (upper lobe and middle lobe) the bronchus was designated eparterial. If it crossed above all bronchi (specifically the upper lobe bronchus) the bronchus was designated hyparterial.[10]

In this way, 44 specimens were obtained with isomeric bronchi (that is bilateral hyparterial or eparterial bronchi). In a further specimen one bronchus was presumed hyparterial since the lung removed at necropsy was bilobed, and the other bronchus was definitely hyparterial. There were six further specimens with lateralised bronchi, in all of which the presence of splenic abnormalities or anomalies of abdominal situs not corresponding with thoracic situs had raised doubts about whether atrial situs was isomeric or lateralised.

These 51 specimens were all arranged so that only the atrial appendages could be seen and then RHA assessed atrial morphology, "blind" without any other knowledge of the specimen. In all six patients with lateralised bronchi, assessment of atrial morphology from the external appearance of the appendages alone indicated lateralised situs, which was confirmed on inspection of the internal anatomy of the atria. The atrial situs corresponded to bronchial situs in all six, and was solitus in four and inversus in two. These hearts are not described further.

In the remaining 45 specimens, atrial morphology was assessed from the external appearance of the appendages alone in 39, and the internal morphology was not examined until later. After inspection of the internal morphology in the remaining six, atrial isomerism was diagnosed in all 45 patients (see Results).

In 20 of these specimens the abdominal viscera remained attached to the specimen, making precise identification of abdominal situs and venous drainage below the diaphragm easy. In the remainder, such information was gleaned from the necropsy reports, from descriptions of cardiac catheterisation, and from angiocardiography or venography.

The data were then punched on to cards and analysed through the University of London Computer Centre, using the *Statistical package for the social sciences*[11] employing the χ^2 and Fisher's exact test for cross-tabulation.

Results

MORPHOLOGY OF BRONCHI (Fig. 1)

All cases with two lungs had isomeric bronchi. In 34 they were of right morphology and in 10, of left. The remaining case had a left bronchus in one lung and was said to have had a bilobed lung on the other side.

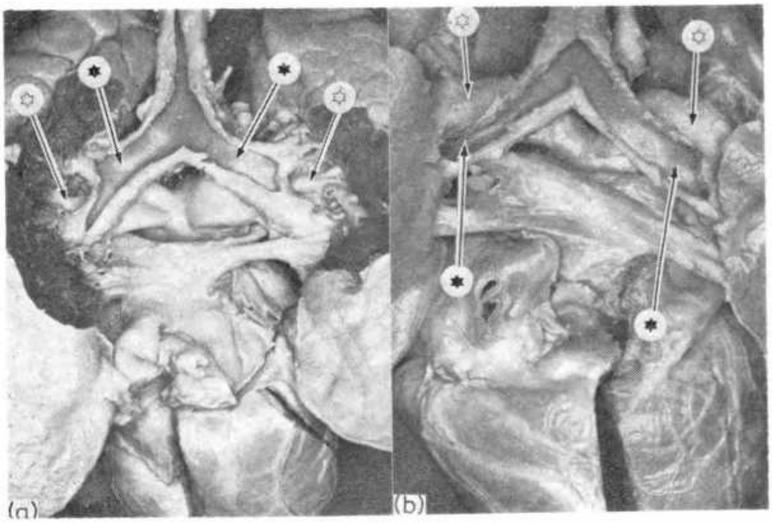

Fig. 1 *Photographs illustrating the difference between isomeric bronchi of right morphology (Fig. 1a) and isomeric bronchi of left morphology (Fig. 1b). The bronchi of right morphology (closed star) are short and the pulmonary arteries continuing their lower lobe branches pass between the first branches of the bronchi and the intermediate stem bronchi. The bronchi of left morphology (Fig. 1b) are both long (closed stars) and the pulmonary artery supplying the lower lobes curves over the bronchi before they give their first (upper lobe) branch (open stars).*

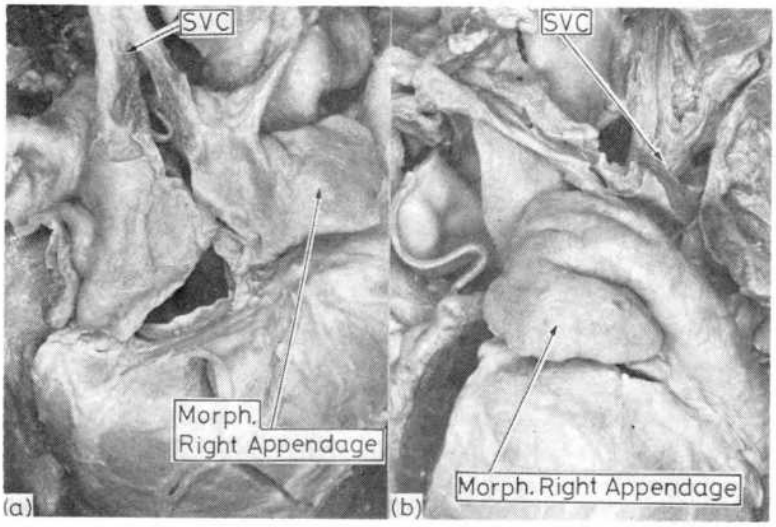

Fig. 2 *Photographs of the atrial appendages from a heart with situs ambiguus and right isomerism. Both appendages are blunt and both join with the atrial chamber along a broad front. Though there is a fold in the left-sided morphologically right appendage (Fig. 2b) it can clearly be seen that this is still a blunt appendage and is of right morphology. SVC, superior vena cava.*

In several cases with bilateral eparterial bronchi, the right upper lobe pulmonary artery originated early (as frequently occurs in normal individuals)[12] and gave the erroneous initial impression that the bronchus was hyparterial since it lay below the right upper lobe pulmonary artery. Once dissection had been carried immediately distal to the first bifurcation of the main bronchus, unequivocal diagnosis of the bronchial morphology was straightforward. In two patients, there was a pre-eparterial bronchus on each side (designated as morphologically right).

MORPHOLOGY OF ATRIA (Fig. 2 to 4)
This was determined on the shape of the atrial appendages, and the morphology of the junction of the trabecular part of the appendage with the smooth walled parts of the atria. Venous connections and septal morphology were not considered because the venous connections were frequently bilateral and the coronary sinus usually absent, while the atrial septum was frequently severely reduced in size or absent.

An atrial chamber was considered to have right atrial morphology when its appendage was blunt,

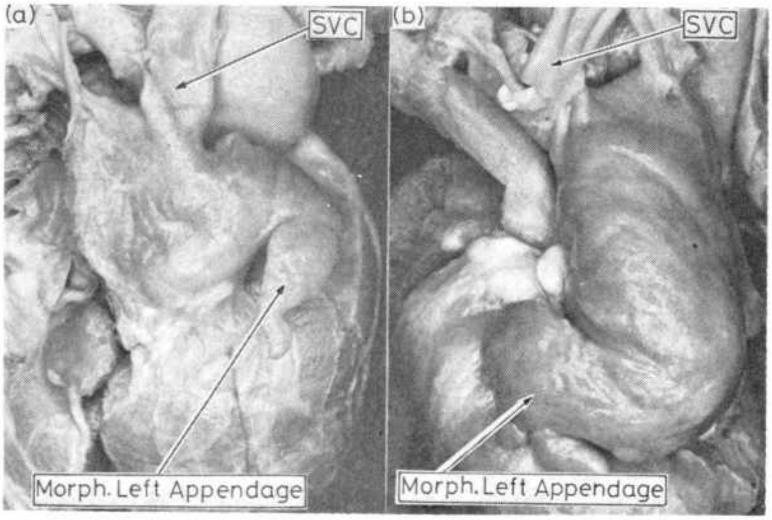

Fig. 3 *Photographs showing the morphology of the atrial appendages in a heart with situs ambiguus and left isomerism. Both appendages are narrow and sinuous and join with the atrial chamber along a narrow front. Abbreviations as before.*

and had a broad junction with the smooth walled atrium. This type of junction was marked by a prominent muscle band protruding into the cavity of the chamber, the crista terminalis.

Left atrial morphology was considered present when the left atrial appendage was long and thin with constrictions along its length. Such appendages had a more constricted junction with the smooth atrium. Though when such left atrial chambers were dilated, the junction had a pectinate appearance, a prominent crista terminalis was not identified. In all the hearts studied, two atrial chambers were identified, on the basis of there being two atrial appendages, each with a junction with the smooth-walled portion of the atrium. These atrial chambers were always both of the same morphology, either right morphology (right atrial isomerism) or left morphology (left atrial isomerism). This is not to be construed as indicating the presence of two normal right or left atria, simply that the atrial chambers had bilateral morphological characteristics of right or left type.

CORRELATION OF ATRIAL WITH BRONCHIAL MORPHOLOGY

In one of the 39 specimens assessed externally, initial examination of the atrial appendages led to an incorrect diagnosis of situs solitus. This was because the right-sided atrial appendage had been rendered blunt by atriotomy at attempted surgical repair of a complete atrioventricular defect. When the internal anatomy was subsequently reviewed, it was clear that there was left isomerism. In the remaining 38, atrial morphology assessed from external appearance alone corresponded with bronchial morphology.

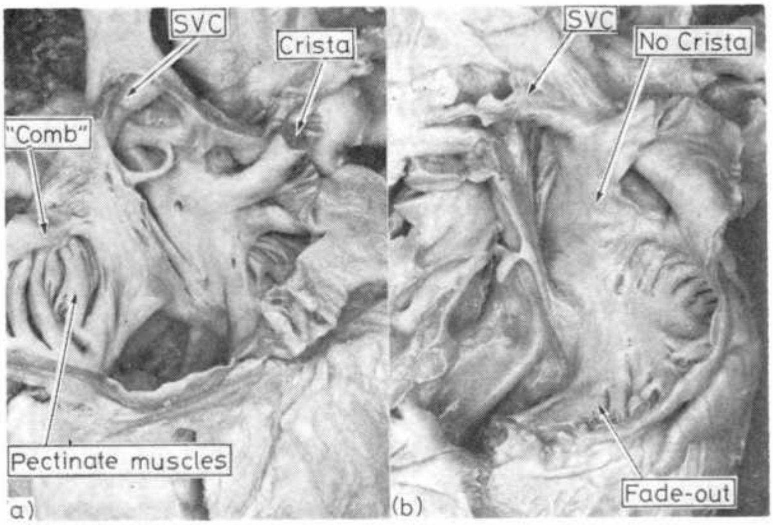

Fig. 4 *The opened right-sided atrial appendages illustrated in Fig. 2a and 3a. The atria of right morphology (Fig. 4a) shows clearly a well-formed crista separating superior vena cava from the atrial appendage. Note that the posterior continuation of the crista has pectinate muscles inserted along its length producing an appearance reminiscent of a comb. This arrangement is not seen in the morphologically left atrium illustrated in Fig. 4b. In addition there is no crista separating the pectinate muscles of the atrial appendage from the superior vena cava in this atrium. The pectinate muscles are anteriorly positioned and fade out as they pass posteriorly. This is in contradistinction to the comb-like appearance illustrated in Fig 4a in the morphologically right atrial chamber.*

In the six patients in whom the external appearances of the atrial appendages were equivocal, the internal anatomy of the atria was viewed with the remainder of the heart still hidden. In one of these hearts, inversus atria were diagnosed on blind assessment in the presence of bilateral hyparterial bronchi. On review, it appeared that a flap of atrial tissue had been mistaken for crista terminalis, so the final diagnosis was left isomerism. In the remaining five, atrial morphology corresponded unequivocally with bronchial morphology.

In summary, no case was found with isomeric bronchi which did not have isomeric atria.

ATRIAL MORPHOLOGY AND OTHER INDICANTS OF SITUS

(a) *Lung lobulation* (Table 1)

Though there was a highly significant association between bilobed lung and left atrium and trilobed lung and right atrium, there was a 14·4 per cent failure rate of lung lobulation as a predictor of atrial situs.

Table 1 *Atrial anatomy and lung lobulation*

	Right atrium	*Left atrium*
Bilobed lung	7 (30%)	16 (70%)
Trilobed lung	61 (91%)	6 (9%)

(b) *Splenic status* (Table 2)

Polysplenia was strongly associated with left isomerism, and asplenia with right isomerism ($p < 0{\cdot}0001$). Nevertheless there were four of 38 cases (10·5%) with a single spleen who had right isomerism, with the spleen hypoplastic in only one. Furthermore, in three out of 10 cases (30%) with left isomerism, there was a single spleen. There were thus seven out of 38 patients (18·4%) in whom atrial isomerism was not associated with either asplenia or polysplenia. One patient with polysplenia had right isomerism.

Table 2 *Spleen in atrial isomerism*

	Single (R)	*Single (L)*	*Multiple (R)*	*Multiple (L)*	*Absent*
Right isomerism*	2 (7%)	2 (7%)	1 (4%)	0	23 (82%)
Left isomerism†	1 (10%)	2 (20%)	2 (20%)	5 (50%)	0

* Six splenic state unknown.
† One splenic state unknown.

(c) *Hepatic position* (Table 3)

This was lateralised in 20 of 37 patients (54·1%) in whom it was recorded.

Table 3 *Liver position in atrial isomerism*

	Right	*Left*	*Central*	*Unknown*
Right isomerism	7 (26%)	6 (22%)	14 (52%)	7
Left isomerism	4 (40%)	3 (30%)	3 (30%)	1

$\chi^2 = 1{\cdot}4$ (not significant).

(d) *Gastric position*

There was no pattern noted for gastric position in the series as a whole. In any individual case, this was often variable because the stomach was suspended on a long dorsal mesogastrium, and could move easily from one side to the other.

(e) *Gall bladder*

This was absent in one case with left isomerism out of eight in which its morphology had been noted.

SYSTEMIC VENOUS RETURN

An *interrupted inferior vena cava* (Table 4) occurred in seven out of 11 patients (63·6%) with left isomerism, and in none with right isomerism. The *hepatic veins* (Table 5) frequently either straddled the atrial septum, or drained separately to both atria or both sides of a common atrium.

Table 4 *Azygos continuation in atrial isomerism*

	None	*Right*	*Left*
Right isomerism	34 (100%)	0	0
Left isomerism	4 (36%)	1 (9%)	6 (55%)

$\chi^2 = 25{\cdot}6$ ($p < 0{\cdot}0001$).

The *superior venae cavae* were bilateral in 20 out of 45 patients (44·4%), there being an atretic cord on one side and a patent vessel on the other in a further three. In only one patient (with left isomerism) did one superior vena cava (the left) drain to a coronary sinus. In all others, the coronary sinus was absent, and the superior venae cavae drained to the "top corners" of the atria in close proximity to the atrial appendage. No patient with right isomerism had a coronary sinus, though two with left isomerism did. The type of isomerism was not associated at a statistically significant level with either absence of the coronary sinus or bilateral superior vena cava.

Table 5 *Hepatic venous drainage in atrial isomerism*

	Unilateral	*Bilateral*	*Straddling*
Right isomerism	25 (73%)	6 (18%)	3 (9%)
Left isomerism	8 (73%)	2 (18%)	1 (9%)

$\chi^2 = 0{\cdot}003$ (not significant).

PULMONARY VENOUS RETURN

In seven out of 11 patients (63·6%) with left isomerism, two pulmonary veins returned to each atrium or each side of a common atrium, whereas in the remainder all pulmonary veins drained to one atrium. Bearing in mind that there were

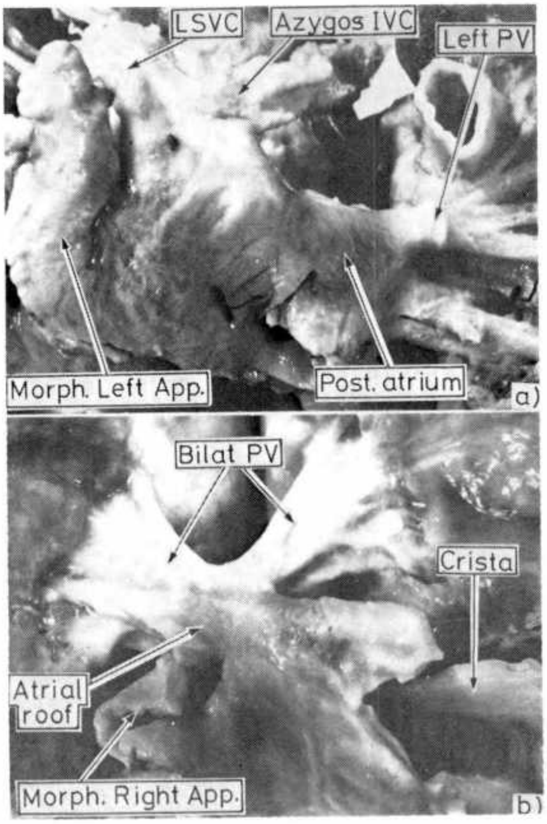

Fig. 5 *Photographs illustrating the different mode of insertion of the pulmonary veins into the atrial chambers in left isomerism and right isomerism. Fig. 5a shows the left-sided atrial chamber (of left atrial morphology) in a patient with left isomerism. The left superior vena cava is seen entering the roof of the atrium between the appendage and a broad posterior atrial wall. There is azygos continuation for the inferior vena cava to the left-sided cava. The pulmonary veins enter the broad posterior wall of the chamber with a considerable distance between left pulmonary veins and the cava and between left pulmonary veins and right pulmonary veins (not visible in this photograph). Fig. 5b shows the drainage of the pulmonary veins from both lungs (bilat PV) to the roof of the atrial chambers in a patient with situs ambiguus and right isomerism. Note the right-sided crista. The pulmonary veins enter closely together into the roof of the atrial chambers, and are quite differently inserted from either the normal heart or the patient illustrated with left isomerism.*

bilateral left atria, pulmonary venous drainage could be regarded as normal, particularly in the way the veins returned to the heart. There was the normal wide area of posterior atrial wall between the pulmonary veins when the heart was viewed from the back (Fig. 5a)

In contrast, pulmonary venous return was anomalous in all but one patient (97·0%) with right isomerism. The site of pulmonary venous return was unknown in one, but was presumably anomalous, since no pulmonary veins were seen entering the atria. In eight patients out of 33 (24·2%), though the veins returned to one or other atrium or a common atrium, the connection with the heart was abnormal in that, viewed from behind, there was a very small area of atrial wall between the points of entry of the pulmonary veins (Fig. 5b). In three of these patients the veins became confluent before entry into the atrial mass via a single, obstructed, common vein. In a further patient half the pulmonary veins returned to the atrial mass and half to the portal vein. The sites of pulmonary venous return in right isomerism are given in Table 6. Table 7 compares pulmonary venous return in the two forms of isomerism.

Table 6 *Pulmonary venous drainage in atrial isomerism*

Superior vena cava	9
Infradiaphragmatic (6 portal)	8
Atrium	8
Mixed	6
Vertical vein	2
	33
Unknown	1

Pulmonary venous return was judged obstructed on anatomical grounds in 12 out of 31 cases (38·7%) of right isomerism. In three cases it was not known whether there was any obstruction.

Table 7 *Anomalous pulmonary venous drainage in atrial isomerism*

	None	*Partial*	*Complete*	*Unknown*
Right isomerism	1 (3%)	0	32 (97%)	1
Left isomerism	4 (36%)	7 (64%)	0	0

$\chi^2 = 39{\cdot}7$ ($p < 0{\cdot}001$).

OVERALL VENOUS RETURN

We defined a "solitus" venous connection as one in which the systemic veins drained to the right-sided atrium (or right side of a common atrium) and the pulmonary veins drained to the left-sided atrium (or left side of a common atrium). An "inversus" connection was the inverse of the above. Otherwise the venous connection was termed "ambiguous". An "ambiguous" connection was extremely common (Table 8).

ATRIAL SEPTATION

In 14 patients with right isomerism (42·4%), and in none with left isomerism, there was a simple, narrow, strand of atrial tissue running across the atrial cavity from immediately anterior to a common atrioventricular orifice to the posterior atrial wall a little above the common atrioventricular orifice (Fig. 6). In four further patients with right isomerism, this simple strand became an extended strand by broadening out superiorly and inferiorly at its posterior end. The superior end of the extension ran to a point just medial to the entry of one superior vena cava, and the inferior end ran to a point just medial to the entry of a hepatic vein.

In two patients with right isomerism there was a superior rim of atrial septum only, less than 2 mm in depth.

The degree of atrial septation is shown in Table 9. For the purpose of assessing the haemodynamic state, a common atrium was held to be present when the maximum extent of the atrial septum was a superior rim or extended strand. Thus common atrium was present in 25 (56·8%) cases, 21 with right isomerism and four with left isomerism.

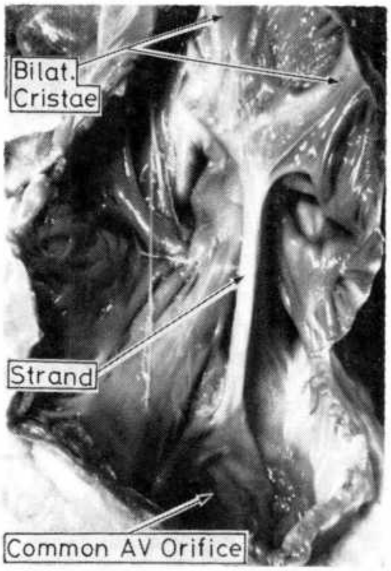

Fig. 6 *Photograph of the atrial chambers opened from behind and retracted upwards in a patient with situs ambiguus and right isomerism. The bilateral cristae are seen in the roof of the atrium. There is a common atrioventricular orifice draining both atrial chambers to the ventricular mass. The atrial chamber is crossed by a strand of tissue passing from the posterior atrial wall to the anterior atrioventricular junction. This is the only evidence of a septum in these atrial chambers.*

Table 8 *Venous connections in atrial isomerism*

	"Solitus"	*"Inversus"*	*"Ambiguus"*
Right isomerism*	0	1 (3%)	32 (97%)
Left isomerism	2 (18%)	1 (9%)	8 (73%)

* Pulmonary venous return unknown in one.

OVERALL MIXING OF VENOUS RETURN

In an attempt to correlate anatomy with haemodynamics, we presumed that if there was a common atrium or an "ambiguous" venous connection or an absent or imperforate atrioventricular valve, there would be complete mixing of venous return from the body and lungs. Otherwise there would be streaming.

Thus defined, complete mixing was present in 44 out of 45 patients (97·8%). The only patient in whom streaming was present at atrial level also had pulmonary atresia, and therefore complete mixing at ventricular/great artery level.

HEART POSITION

The main bulk of the heart was to the right in 13 out of 45 patients (28·9%), to the left in 31 out of 45 (68·9%), and in the middle in one. There was no significant difference between right and left isomerism in this respect.

AGE AT DEATH

The median ages at death were 1·1 months for right isomerism and 1·75 months for left isomerism.

Discussion

The cardiac lesions associated with visceral heterotaxy are of extreme complexity, so, for the sake of clarity, we have restricted ourselves in this presentation to consideration of visceral situs, venous return to the heart, and atrial morphology. The anatomy from the atrioventricular valves downstream is described elsewhere.[13]

It is now generally agreed[4 8 14 15] that the method of sequential chamber localisation introduced by Van Praagh *et al.*[16] is the best way of classifying congenital heart disease. This method starts with,

Table 9 *Atrial septum in atrial isomerism*

	None	*Strand*	*Superior rim only*	*Primum ASD*	*PFO or intact*
Right isomerism	1 (3%)	18 (55%)	2 (6%)	9 (27%)	3 (9%)
Left isomerism	4 (36%)	0	0	5 (46%)	2 (18%)

ASD, atrial septal defect; PFO, patent foramen ovale.

and is therefore, founded upon, the identification of atrial situs. Yet no agreement exists on how many types of atrial situs exist. While all aver that situs solitus and inversus are discrete entities, some have suggested[17] that these two categories alone may be sufficient. Others have added situs indeterminatus,[1 15 16] either encompassing both polysplenia and asplenia[1 15] or else excluding polysplenia.[16] Others maintain that situs ambiguus consists of two separate entities, categorised either as asplenia and polysplenia[3 4] or as right and left isomerism.[7 9]

We suggest that the relative merits of these alternatives can be assessed by asking the following four questions, in descending order of importance. Can they be reliably distinguished; are they based upon anatomical facts; are they of more than academic importance; and do they relate to the heart?

The concept of there being only two forms of atrial situs[17] falls at the first fence. This is because the suggested criterion for the morphologically right atrium is the termination of the supradiaphragmatic inferior vena cava.[18] If there are only two types of situs, then it is essential to be able to trace the inferior vena cava to either one or the other atrium. But our series includes four patients in whom the supradiaphragmatic inferior vena cava straddled the atrial septum to connect with both atria. In a further five patients, the inferior vena cava was interrupted and hepatic veins separately entered both atria. There was no way in these cases of deciding which hepatic vein was in reality the supradiaphragmatic inferior vena cava. So all of these patients, according to the criterion of drainage of the vena cava, had right isomerism, which is neither situs solitus nor inversus. There must therefore be at least three types of situs. But are these three types solitus, inversus, and asplenia (right isomerism)?

If the asplenia syndrome is the only form of situs indeterminatus (ambiguus), then all cases of "polysplenia" must have situs solitus or situs inversus. This proposition would not account for the distinctive morphological appearances of the atria in left isomerism[3 4 9] confirmed by our own studies, nor for the abnormal site and size (or even absence) of the sinus node in this condition.[19] Even if atrial morphology were ignored, it would be impossible on this basis to classify patients with polysplenia who had the abnormalities of inferior vena caval and hepatic venous drainage described above. The very fact that "polysplenia" is neither situs solitus nor inversus nor asplenia means that a further category of situs is necessary. Therefore, is "polysplenia" a variety of situs ambiguus? Since it forms a syndrome characterised not only by abdominal and thoracic abnormalities, but also by a constellation of cardiac defects, we agree with Stanger *et al.*[4] that it is indeed a variety of situs ambiguus.

We are then left with the question of how to subdivide and describe those patients who have neither atrial situs solitus nor inversus. The strongest argument in favour of retaining the blanket term "situs indeterminatus" would be that it is an honest recognition of uncertainty. This concept seems to us to have great merit in describing general visceral situs. Our study has confirmed repeated observations by others,[1 3 4 20–22] that there is no consistent pattern of arrangement of either abdominal viscera or even of lung lobes in situs ambiguus. In short, there is visceral heterotaxia. But our results also show that this uncertainty need not be extended to encompass the bronchi and atria. The importance of bronchial anatomy in visceral heterotaxy was first noted by Brandt and Liebow,[10] and subsequently confirmed in small series of patients by others.[22–24] The only large series of personally studied patients with situs ambiguus in whom bronchial anatomy was reported is that by Stanger *et al.*,[4] who found isomeric bronchi in all of 35 patients with asplenia or polysplenia. We have found bronchial isomerism in all of 45 patients with isomeric atria. Thus, though one case has been described in which the patient had asplenia and isomeric atria but solitus bronchi,[9] there does appear to be very great general consistency in the bronchial branching pattern in situs ambiguus. Furthermore this takes two distinct forms, one with bilateral right, and one with bilateral left bronchi.

As to the consistency of atrial morphology, there is no question that in individual cases of visceral heterotaxy, the general disturbance of atrial anatomy can make identification of the atria difficult. But by assessing the morphology blind, and including patients with lateralised situs as well as those with atrial isomerism in the assessment, we have shown that an experienced observer can reliably identify atrial isomerism. Since that assessment corresponded exactly to bronchial morphology, and because it was so different for patients with on the one hand, anomalous pulmonary venous return, and on the other hand interruption of the inferior vena cava, we contend that right and left atrial isomerism are biological and anatomical realities and not simply "convenient mnemonics".[2]

This view is supported by examination of the conduction system.[19 23 25] Right isomerism is characterised by bilateral sinus nodes, which are right-sided structures, whereas in left isomerism the node is either absent or else displaced and hypoplastic.

For the reasons outlined we endorse wholeheartedly the view[4] that situs ambiguus should be divided into two categories. We do not consider, however, that "polysplenia" and "asplenia" are the optimal terms for these sub-categories. It is our preference to divide atrial situs ambiguus into right isomeric and left isomeric forms. There are many reasons for this.

Firstly, we lose no accuracy in predicting other associated cardiac anomalies. All the associations we have shown with right isomerism have previously been described for asplenia[3 4 23 26 27] while those for left isomerism have been described for polysplenia.[3 4 22 26] This applies not only to anomalies of venous connections and atrial morphology presently described but also to the anatomy of the atrioventricular valves and the region distal to them.[13]

Secondly, we are describing a segment of the heart, which is surely more appropriate for a cardiac nomenclature than one incorporating a description of the spleen.[4]

Thirdly, the relation between left isomerism and polysplenia, right isomerism and asplenia is close, but not one to one. Indeed we found 18·4 per cent of patients with isomeric atria and bronchi who did not have asplenia or polysplenia. The asplenia syndrome without asplenia (sic!) has also been described by others.[3 28]

Finally, diagnostic "labels" affect the way in which patients are investigated. Cardiologists are becoming accustomed to being able to attach exceedingly accurate diagnostic labels to their patients. The label "polysplenia" cannot be attached with certainty until the diagnosis of polysplenia is established. Since this is not always possible with splenic scintigraphy because of inadequate resolution,[5 29 30] the temptation is to proceed to splenic arteriography.[31] This we regard as unfortunate, because as far as we know, polysplenia per se does not harm the patient and its demonstration will not affect management. By contrast, it is very important to know before cardiac catheterisation whether or not there is left or right isomerism because this immediately enables a number of predictions to be made about the cardiac anatomy. The value of recognition of a strong possibility of total anomalous pulmonary venous return or interruption of the inferior vena cava before cardiac catheterisation has already been stressed.[5 32]

It has been shown that bronchial visualisation provides a completely objective means of assessing bronchial morphology,[5] and that this is usually simple even in infants.[32] These studies provide the proof that this in turn reliably predicts atrial morphology. We accept that occasional exceptions to this rule exist,[4 8 9] but their existence is no reason for carrying out selective atrial appendage injections of contrast medium[8] in every patient. Rather, these should be performed when there are good grounds for suspecting a failure of prediction, for example, a hypothetical patient with laevocardia, a patent foramen ovale, normally related ventricles, and normally connected great arteries, who has isomeric right bronchi.

RELEVANCE OF ASPLENIA

While we take the view that splenic status is irrelevant to the segmental description of the heart, this is not to suggest that it does not matter to the patient, since asplenia carries with it an increased risk of overwhelming infection, particularly by the pneumococcus, and long-term prophylactic antibiotics may be indicated.[33] In several of the patients known to have asplenia in this study, Howell-Jolly bodies were sought in the peripheral blood and not found, so they are not completely reliable as predictors of asplenia. We suggest therefore that patients with either isomeric right bronchi or persistent Howell-Jolly bodies in the blood smear should be considered for long-term antibiotics on the presumption that they have asplenia or splenic hypoplasia.

EFFECT UPON THE TYPES OF ATRIOVENTRICULAR CONNECTION

Use of the terms "concordant" and "discordant" to describe the atrioventricular connection was first introduced by Van Praagh *et al.*[16] but then abandoned because they were not applicable in situs ambiguus.[2] We have retained them[14] because they convey anatomical and haemodynamic information. In the majority of cases of atrial isomerism[13] the type of atrioventricular connection can be very simply described as double inlet, absent left connection, or absent right connection.[14] It is only in those hearts with two ventricles that the problem arises.

As indicated in the introduction, if it could be shown that the venous return in atrial isomerism could be considered lateralised, then the terms concordant and discordant could still justifiably be used. Our results show conclusively that this is not the case. The anatomy in all but one patient (97·8%) was such that complete mixing of pulmonary and systemic venous blood would have occurred at atrial level. For this reason, we see no alternative to describing the type of atrioventricular connection as ambiguous in hearts with isomeric atria and two ventricles. This term conveys much anatomical information, indicating as it does that two ventricles are present. And no haemodynamic information is lost in the majority of cases, because pulmonary and systemic venous blood have already mixed completely at atrial level. There may be a tiny minority of patients in whom further brief haemodynamic information might be useful.

An example would be a patient with an anomaly resembling in every way a typical ostium primum atrial defect except that there was interruption of the inferior vena cava with right-sided azygos continuation, left isomerism, and polysplenia. To describe this heart as left isomerism-ambiguous-concordant (quasi normal situs and connections) conveys considerably more information than the pure segmental notation, whether this be ambiguous-ambiguous-concordant,[14] polysplenia-d-loop(L)-d-normal,[4] or (A-D-S).[34] This extremely rare and eminently soluble problem seems to us a poor reason for abandoning the concept of concordance and discordance[2] which we and others[35] have found most helpful.

References

1 Lev M, Liberthson RR, Eckner FAO, Arcilla RA. Pathologic anatomy of dextrocardia and its clinical implications. *Circulation* 1968; **37**: 979–99.

2 Van Praagh R. Terminology of congenital heart disease. Glossary and commentary. *Circulation* 1977; **56**: 139–43.

3 Van Mierop LHS, Gessner IH, Schiebler GL. Asplenia and polysplenia syndrome. *Birth Defects* 1972; **8**, no 1: 74–82.

4 Stanger P, Rudolph AM, Edwards JE. Cardiac malpositions. An overview based on study of sixty-five necropsy specimens. *Circulation* 1977; **56**: 159–72.

5 Partridge JB, Scott O, Deverall PB, Macartney FJ. Visualisation and measurement of the main bronchi by tomography as an objective indicator of thoracic situs in congenital heart disease. *Circulation* 1975; **51**: 188–96.

6 Van Mierop LHS, Eisen S, Schiebler GL. The radiographic appearance of the tracheobronchial tree as an indicator of visceral situs. *Am J Cardiol* 1970; **26**: 432–5.

7 Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977*. Edinburgh: Churchill Livingstone, 1978: 16–26.

8 Brandt PWT, Calder AL. Cardiac connexions: the segmental approach to radiologic diagnosis in congenital heart disease. *Curr Probl Diagn Radiol* 1977; **7**: 1–35.

9 Caruso G, Becker AE. How to determine atrial situs? Considerations initiated by three cases of absent spleen with a discordant anatomy between bronchi and atria. *Br Heart J* 1979; **41**: 559–67.

10 Brandt HM, Liebow AA. Right pulmonary isomerism associated with venous, splenic and other anomalies. *Lab Invest* 1958; **7**: 469–504.

11 Nie NH, Hull CH, Jenkins JG, Steinbrenner K, Bent DH. *Statistical package for the social sciences.* 2nd ed. New York: McGraw-Hill, 1975.

12 Liebow AA, Hales MR, Bloomer WE. Relation of bronchial to pulmonary vascular tree. In: Adams WR, Veith I, eds. *Pulmonary circulation.* New York: Grune & Stratton, 1959: 79–98.

13 De Tommasi SM, Daliento L, Ho SY, Macartney FJ, Anderson RH. Analysis of atrioventricular junction, ventricular mass, and ventriculoarterial junction in 43 specimens with atrial isomerism. *Br Heart J* 1981. (In press).

14 Tynan MJ, Becker AE, Macartney FJ, Quero-Jiménez M, Shinebourne EA, Anderson RH. Nomenclature and classification of congenital heart disease. *Br Heart J* 1979; **41**: 544–53.

15 Anselmi G, Muñoz S, Blanco P, Machado I, de la Cruz M. Systematisation and clinical study of dextroversion, mirror-image dextrocardia, and laevoversion. *Br Heart J* 1972; **34**: 1085–98.

16 Van Praagh R, Van Praagh S, Vlad P, Keith JD. Anatomic types of congenital dextrocardia. Diagnosis and embryologic implications. *Am J Cardiol* 1964; **13**: 510–31.

17 Van Praagh R. Segmental approach to diagnosis in congenital heart disease. *Birth Defects* 1972; **8**: No. 5; 4–23.

18 Leachman RD, Angelini P, Cokkinos DV. Hepato-atrial dissociation. Report of two cases and clinical implications. *Chest* 1973; **63**: 926–32.

19 Dickinson DF, Wilkinson JL, Anderson KR, Smith A, Ho SY, Anderson RH. The cardiac conduction system in situs ambiguus. *Circulation* 1979; **59**: 879–85.

20 Lev M, Liberthson RR, Golden JG, Eckner FAO, Arcilla RA. The pathologic anatomy of mesocardia. *Am J Cardiol* 1971; **28**: 428–35.

21 Liberthson RR, Hastreiter AR, Sinha SN, Bharati S, Novak GM, Lev M. Levocardia with visceral heterotaxy-isolated levocardia: pathologic anatomy and its clinical implications. *Am Heart J* 1973; **85**: 40–54.

22 Moller JH, Nakib A, Anderson RC, Edwards JE. Congenital cardiac disease associated with polysplenia. *Circulation* 1967; **36**: 789–99.

23 Van Mierop LHS, Wiglesworth FW. Isomerism of the cardiac atria in the asplenia syndrome. *Lab Invest* 1962; **11**: 1303–15.

24 Landing BH, Lawrence T-YK, Payne VC, Jr, Wells TR. Bronchial anatomy in syndromes with abnormal visceral situs, abnormal spleen and congenital heart disease. *Am J Cardiol* 1971; **28**: 456–62.

25 Bharati S, Lev M. The course of the conduction system in dextrocardia. *Circulation* 1978; **57**: 163–71.

26 Rose V, Izukawa T, Moës CAF. Syndromes of asplenia and polysplenia. A review of cardiac and non-cardiac malformations in 60 cases with special

reference to diagnosis and prognosis. *Br Heart J* 1975; **37**: 840–52.

27 Ivemark BI. Implications of agenesis of the spleen on the pathogenesis of cono-truncus anomalies in childhood. *Acta Paediatr Scand* 1955; **44**, suppl 104: 1–110.

28 Layman TE, Levine MA, Amplatz K, Edwards JE. "Asplenic syndrome" in association with rudimentary spleen. *Am J Cardiol* 1967; **20**: 136–40.

29 Freedom RM, Treves S. Splenic scintigraphy and radionuclide venography in the heterotaxy syndrome. *Radiology* 1973; **107**: 381–6.

30 Randall PA, Moller JH, Amplatz K. The spleen and congenital heart disease. *Am J Roentgenol* 1973; **119**: 551–9.

31 Vaughan TJ, Hawkins IF Jr, Elliott LP. Diagnosis of polysplenia syndrome. *Radiology* 1971; **101**: 511–8.

32 Deanfield JE, Leanage R, Stroobant J, Chrispin AR, Taylor JFN, Macartney FJ. Use of high kilovoltage filtered beam radiographs for detection of bronchial situs in infants and young children. *Br Heart J* 1980; **44**: 577-83.

33 Waldman JD, Rosenthal A, Smith AL, Shurin S, Nadas AS. Sepsis and congenital asplenia. *J Pediatr* 1977; **90**: 555–9.

34 Van Praagh R, Weinberg PM, Van Praagh S. Malposition of the heart. In: Moss AJ, Adams FH, Emmanouilides GC, eds. *Heart disease in infants, children and adolescents.* Baltimore: Williams & Wilkins, 1977: 394.

35 Kirklin JW, Pacifico AD, Bargeron LM Jr, Soto B. Cardiac repair in anatomically corrected malposition of the great arteries. *Circulation* 1973; **48**: 153–9.

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Br Heart J 1980; **44**: 668–71

Correlation between changes in systolic time intervals and left ventricular end-diastolic diameter after preload reduction

*Non-invasive monitoring of pharmacological intervention**

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SUMMARY In order to measure the effect of a decrease in preload on systolic time intervals and left ventricular end-diastolic diameter (LVEDD) measured by echocardiography, eight healthy young subjects were given 40 mg frusemide intravenously. The pre-ejection period index (PEPI) increased and the left ventricular end-diastolic diameter decreased. A correlation between ΔPEPI and ΔLVEDD was shown. Using changes in systolic time intervals in the evaluation of changes in contractility it is important to correct for changes in preload. For normal subjects it is suggested that the relation between ΔPEPI and ΔLVEDD as a percentage of the mean values should be used for this correction. A method is suggested for estimating the changes in pre-ejection period index induced by changes in left ventricular end-diastolic diameter.

Systolic time intervals are influenced by preload, afterload, and myocardial contractility.[1–3] Thus, given a constant pre- and afterload or provided that the relative influence of pre- and afterload can be accounted for, changes in systolic time intervals can be used as an indicator of changes in myocardial contractility.

No feasible method exists for measuring preload non-invasively. Alterations in left ventricular end-diastolic diameter, however, can be used as an indicator of changes in preload,[4] especially in acute studies where changes in myocardial compliance, not caused by volume changes, may be considered minimal.

The present study was undertaken in order to examine whether a preload reduction induced by frusemide, 40 mg intravenously, would cause a decrease in left ventricular end-diastolic diameter detectable by quantitative echocardiography.

Simultaneous measurements of systolic time intervals were performed in order to investigate whether an expected decrease in cardiac performance, as recorded by systolic time intervals, could be correlated with left ventricular end-diastolic diameter.

Subjects and methods

Eight healthy subjects, five male and three female, aged 21 to 28 years, volunteered for the study by written informed consent. After voiding urine, they were weighed and control recordings of systolic time intervals, left ventricular end-diastolic diameters, and blood pressures were made.

Frusemide, 40 mg, was given intravenously. After 15 and 30 minutes repeated measurements of systolic time intervals, left ventricular end-diastolic diameter, blood pressure, weight, and diuresis were performed.

Systolic time intervals were recorded at a paper speed of 100 mm/s on a Siemens Mingograph 62 using two Siemens 860 transducers, for phonocardiography and carotid pulse wave tracings.

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During 10 consecutive beats, total electromechanical systole (QS$_{\text{II}}$), left ventricular ejection time (LVET), and pre-ejection period (PEP) were measured and corrected for heart rate (QS$_{\text{II}}$I, LVETI, PEPI).[5] PEP/LVET was calculated from the uncorrected data.

Echocardiography was performed using either an Aloka SSD 11OS-E instrument interphased to a Honeywell 1856A Visicorder or a Mediscan 30 ultrasonic apparatus in combination with a Cambridge multichannel recorder. The echocardiogram was recorded in the left lateral position during normal, quiet respiration. Left ventricular end-diastolic diameter was measured in five consecutive beats immediately inferior to the mitral leaflets at the peak of the electrocardiographic R wave.

The reliability of the measured values was tested as follows. The systolic time intervals were analysed blindly by two observers. The mean interobserver differences were: 0·4 per cent for QS$_{\text{II}}$I, 0·5 per cent for left ventricular ejection time index, 1·1 per cent for pre-ejection period index, and 2·3 per cent for PEP/LVET. In order to avoid interobserver variations, the echocardiograms were analysed blindly by a single observer. Repeated examinations of left ventricular end-diastolic diameter in eight persons with a 10 week interval have previously shown a mean difference of 2·3 per cent (H Egeblad, unpublished data).

Corresponding data for each individual were compared using Student's t test for paired data. Correlations were calculated using Spearman's rank correlation and least square linear correlation. When expressing percentage changes, regression towards the mean was avoided by conventional statistical methods.[6]

Table 1 *Weight, diuresis, pulse rate, and blood pressure ± 1 SEM before and after frusemide*

	Control	*15 min*	*30 min*
Weight (kg)	66·8 ±3·0		65·8 ±3·0
Diuresis (ml)		456 ±79	947 ±67
Pulse rate (beats/min)	71 ±5	68 ±4	66 ±4
Systolic blood pressure (mmHg)	138 ±8	140 ±7	137 ±7
Diastolic blood pressure (mmHg)	81 ±7	84 ±6	83 ±6

Results

The changes in body weight, pulse rate, and blood pressure are seen in Table 1. The variation in pulse rate and blood pressure were not statistically significant. The diuresis (mean ±SEM) was 456 ± 79 ml and 947 ±67 ml after 15 and 30 minutes, respectively. Alterations in systolic time intervals and left ventricular end-diastolic diameter were observed after 15 minutes. For left ventricular end-diastolic diameter, QS$_{\text{II}}$I, and left ventricular ejection time index the changes were not significant until after 30 minutes (Table 2).

The relation between left ventricular end-diastolic diameter and pre-ejection period index is visualised in Fig. 1. The relation between left ventricular end-diastolic diameter and PEP/LVET was similar.

The correlation coefficients between changes in left ventricular end-diastolic diameter (ΔLVEDD) versus changes in systolic time index and diuresis are seen in Table 3. No correlation was found between ΔLVEDD and the absolute diuretic volume or the diuretic volume as a percentage of the initial body weight. A correlation was shown between ΔLVEDD and changes in systolic time intervals, both when a linear and a non-linear

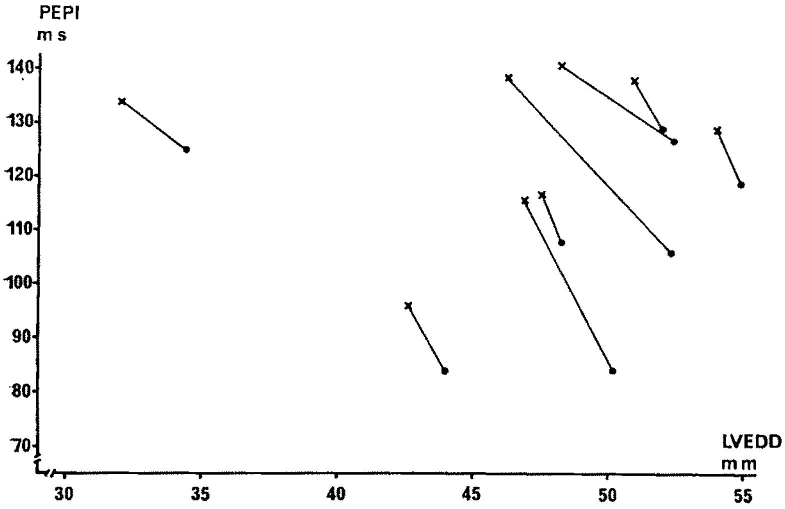

Fig. 1 *Simultaneous measurements of left ventricular end-diastolic diameter (LVEDD) and pre-ejection period index (PEPI) before (●) and 30 minutes after (×) frusemide, 40 mg intravenously.*

Table 2 *Left ventricular end-diastolic diameter and systolic time intervals before and after frusemide (mean ± 1 SEM)*

	Control	*15 min*		*30 min*	
LVEDD (mm)	48·6 ±2·3	46·9 ±2·3	NS	46·1 ±2·3	$p<0·01$
QSnI (ms)	529 ±6	529 ±8	NS	524 ±7	$p<0·05$
LVETI (ms)	419 ±4	410 ±4	NS	397 ±4	$p<0·001$
PEPI (ms)	110 ±6	119 ±5	$p<0·05$	127 ±6	$p<0·005$
PEP/LVET	0·270 ±0·023	0·304 ±0·012	$p<0·05$	0·348 ±0·019	$p<0·005$

method was used (Table 3). The relation between ΔLVEDD as a percentage of the mean value and ΔPEPI as a percentage of the mean value is depicted in Fig. 2.

Discussion

Left ventricular end-diastolic volume and left ventricular end-diastolic diameter are very sensitive to changes in filling pressure, if the ventricle is not overloaded.[4 7 8] In this situation it is therefore possible to use changes in left ventricular end-diastolic diameter as an indicator of changes in preload.

The haemodynamic effects of frusemide are not the result of changes in contractility,[9] but are mainly caused by a decrease in preload.[10 11] According to the Starling principle, a decrease in preload will lead to a decrease in cardiac performance if the left ventricle is not overloaded.[7 12]

The first 30 minutes after frusemide administration the effect on preload is mainly the result of an increase in venous capacitance and only later of a decrease in plasma volume.[10] This offers an explanation of the lack of correlation between ΔLVEDD and diuresis in the present study.

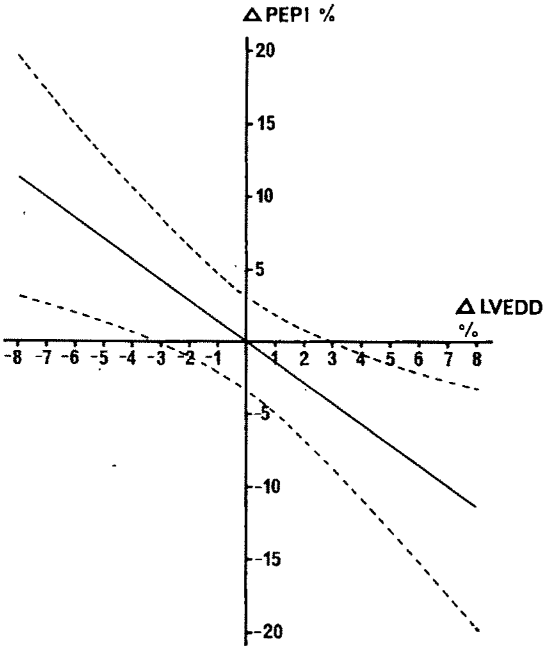

Fig. 2 *The calculated correlation between percentage change in pre-ejection period index (ΔPEPI%) and percentage changes in left ventricular end-diastolic diameter (ΔLVEDD%). The dotted lines represent 95 per cent confidence limits.*

Table 3 *Nonlinear and linear correlation between ΔLVEDD and changes in systolic time intervals and diuresis after both 15 and 30 minutes*

	r_s	p	r	p
ΔLVEDD versus ΔQSnI	0·467	NS	0·249	NS
ΔLVEDD versus ΔLVETI	0·579	$<0·05$	0·569	$<0·05$
ΔLVEDD versus ΔPEPI	−0·708	$<0·01$	−0·660	$<0·01$
ΔLVEDD versus ΔPEP/LVET	−0·711	$<0·01$	−0·666	$<0·01$
ΔLVEDD versus diuresis	−0·158	NS	−0·144	NS

r_s = Spearman's rank correlation coefficient.
r = linear correlation coefficient.

The systolic time intervals with the closest correlation to invasive measurements of myocardial contractility are pre-ejection period index and PEP/LVET.[3 13] This study shows the feasibility of measuring a change in cardiac performance by systolic time intervals and a decrease in left ventricular end-diastolic diameter caused by a decrease in preload after an intravenous dose of 40 mg frusemide.

Similar changes in systolic time intervals[14 15] and left ventricular end-diastolic diameter[16] have been obtained when the decrease in preload was induced by tilting, dialysis, or administration of glyceryl trinitrate. The importance of correlating changes in these indices has not previously been stressed. Using the pre-ejection period index and PEP/LVET for the evaluation of cardiac effects of drugs, it is therefore important to bear in mind that haemodynamic changes, measured by systolic time intervals, may not only be the result of changes in contractility.

In a group of subjects, as in this study, Fig. 2 can be used to estimate whether the haemodynamic effect of a drug or a physiological manoeuvre can be explained by changes in preload or contractility or both. For example, if a drug induces a decrease in left ventricular end-diastolic diameter of 5 per cent, this may cause an increase in pre-ejection period index of 1 to 13 per cent. Thus, only if an increase in pre-ejection period index greater than 13 per cent is encountered, is an additional mechanism such as decreased myocardial contractility necessary to explain the results. This figure will not necessarily be valid for a group of patients with heart disease, with abnormal left ventricular compliance and size.

The present study has shown a statistically significant correlation between a decrease in left ventricular end-diastolic diameter as an indicator of preload and changes in pre-ejection period index and PEP/LVET in normal subjects. We feel confident that combined measurements of systolic time intervals and echocardiographic determinations of left ventricular end-diastolic diameter will improve the ability to evaluate the haemodynamic effects of drugs.

References

1 Harris WS, Schoenfeld CD, Weissler AM. Effects of adrenergic receptor activation and blockade on the systolic preejection period, heart rate, and arterial pressure in man. *J Clin Invest* 1967; **46:** 1704–14.
2 Harley A, Starmer CF, Greenfield JC Jr. Pressure-flow studies in man: an evaluation of the duration of the phases of systole. *J Clin Invest* 1969; **48:** 895–905.
3 Garrard CL Jr, Weissler AM, Dodge HT. The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. *Circulation* 1970; **42:** 455–62.
4 Rankin LS, Moos S, Grossman W. Alterations in preload and ejection phase indices of left ventricular performance. *Circulation* 1974; **51:** 910–15.
5 Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation* 1968, **37:** 149–59.
6 Oldham PD. A note on the analysis of repeated measurements of the same subjects. *J Chronic Dis* 1962; **15:** 969–77.
7 Patterson SW, Piper H, Starling EH. The regulation of the heart beat. *J Physiol* 1914; **48:** 465–513.
8 Burggraf GW, Parker JO. Effects of dextran infusion on left ventricular volume and pressure in man. *Cathet Cardiovasc Diagn* 1978; **4:** 383–90.
9 Poole-Wilson PA, Cobbe SM, Fry CH. Acute effects of diuretics on potassium exchange, mechanical function and the action potential in rabbit myocardium. *Clin Sci Mol Med* 1978; **55:** 555–9.
10 Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJC. Renal and external hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. *N Engl J Med* 1973; **288:** 1087–90.
11 Mond H, Hunt D, Sloman G. Haemodynamic effects of frusemide in patients suspected of having acute myocardial infarction. *Br Heart J* 1974; **36:** 44–53.
12 Crexells C, Chatterjee K, Forrester JS, Dikshit K, Swan HJC. Optimal level of filling pressure in the left side of the heart in acute myocardial infarction. *N Engl J Med* 1973; **289:** 1263–6.
13 Ahmed SS, Levinson GE, Schwartz CJ, Ettinger PO. Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man. *Circulation* 1972; **46:** 559–71.
14 Stafford RW, Harris WS, Weissler AM. Left ventricular systolic time intervals as indices of postural circulatory stress in man. *Circulation* 1970; **41:** 485–92.
15 Bornstein A, Zambrano SS, Morrison RS, Spodick DH. Cardiac effects of hemodialysis: noninvasive monitoring by systolic time intervals. *Am J Med Sci* 1975; **269:** 189–92.
16 Redwood DR, Henry WL, Epstein SE. Evaluation of the ability of echocardiography to measure acute alterations in left ventricular volume. *Circulation* 1974; **50:** 901–4.

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Br Heart J 1980; **44:** 672-3

Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies*

Definition

"Cardiomyopathies are heart muscle diseases of unknown cause".

Classification

Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy

DILATED CARDIOMYOPATHY

The condition is recognised by dilatation of the left or right ventricle, or both ventricles. Dilatation often becomes severe and is invariably accompanied by hypertrophy. Systolic ventricular function is impaired. Congestive heart failure may or may not supervene. Presentation with disturbances of ventricular or atrial rhythm is common and death may occur at any stage.

HYPERTROPHIC CARDIOMYOPATHY†

This condition is characterised by disproportionate hypertrophy of the left ventricle and occasionally also of the right ventricle which typically involves the septum more than the free wall but occasionally is concentric. Typically the left ventricular volume is normal or reduced. Systolic gradients are common.

Inheritance is usually by an autosomal dominant gene with incomplete penetrance. Characteristic morphological changes, usually most severe in the septum, have been described.

RESTRICTIVE CARDIOMYOPATHY

This may exist either with or without obliteration. Restrictive cardiomyopathy includes endomyocardial fibrosis and Löffler's cardiomyopathy (endocarditis parietalis fibroplastica). It is proposed that this condition should be referred to as eosinophilic endomyocardial disease.

Endomyocardial scarring usually affects either one or both ventricles, and restricts filling. Involvement of the atrioventricular valves is common but the outflow tracts are spared. Cavity obliteration is characteristic of advanced cases.

"Unclassified cardiomyopathy" covers a few cases which do not fit readily into any group. This includes some with minor abnormalities in which progression to overt cardiomyopathy may or may not occur. This has been referred to as latent cardiomyopathy.

Specific heart muscle disease

DEFINITION

Heart muscle disease of known cause or associated with disorders of other systems.

Disorders of the myocardium caused by systemic or pulmonary hypertension, coronary artery disease, valvular heart disease, or congenital cardiac anomalies have been excluded. It was felt that further extension of the classification to include these conditions would have so widened its scope as to render it useless.

Classification

INFECTIVE

Viral myocarditis, for example Coxsackie. Rickettsial myocarditis, for example Coxiella. Bacterial, for example staphylococcal. Fungal, for example aspergillus. Protozoal, for example Chagas's. Metazoal, for example filarial.

METABOLIC

Endocrine

Thyrotoxicosis, hypothyroidism, adrenal cortical insufficience, phaeochromocytoma, acromegaly.

Familial storage disease and infiltrations

Haemochromatosis, glycogen storage disease, Hurler's syndrome, Refsum's syndrome, Niemann-Pick disease, Hand-Schüller-Christian disease, Fabry-Anderson disease, Morquio-Ullrich disease.

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*The Task Force met on Monday 23 June 1980 in Paris and was attended by the following: R O Brandenburg, E Chazov, G Cherian, A O Falase, Y Grosgogeat, C Kawai, F Loogen, V Martin Judez, E Orinius, J F Goodwin, E G J Olsen (Chairman), C M Oakley (Rapporteur), Z Pisa (Secretary).
Asymmetrical hypertrophy
Asymmetric septal hypertrophy, etc.

†Previously known as:
Idiopathic hypertrophic subaortic stenosis
Muscular subaortic stenosis
Obstructive cardiomyopathy
Asymmetrical hypertrophy
Asymmetric septal hypertrophy, etc.

Deficiency
Disturbances of potassium metabolism, magnesium deficiency, and nutritional disorders such as Kwashiorkor, anaemia, and beri-beri.

Amyloid
"Primary", "secondary", "familial": hereditary cardiac amyloidosis, familial Mediterranean fever, senile.

GENERAL SYSTEM DISEASES
Connective tissue disorders
Systemic lupus erythematosus, polyarteritis nodosa, rheumatoid arthritis, scleroderma dermatomyositis.

Infiltrations and granulomas
Sarcoidosis, leukaemia.

HEREDOFAMILIAL
Muscular dystrophies
Duchenne, dystrophia myotonica.

Neuromuscular disorders
Friedreich's ataxia.

SENSITIVITY AND TOXIC REACTIONS
Sulphonamides, penicillin, antimony, cobalt, emetine, alcohol, isoprenaline, anthracyclines, irradiation, alcohol.

The majority of specific heart muscle diseases are associated with dilatation of the ventricles but there are many exceptions. Localised infiltrations may cause disturbances of rhythm or conduction without generalised myocardial dysfunction. Amyloid infiltration is associated with a unique haemodynamic fault and glycogen storage disease may be associated with a hypertrophic picture.

Alcoholic heart disease. Heart disease may be associated with a heavy alcohol intake. At present we cannot define a causal versus a conditioning role of alcohol nor apply precise diagnostic criteria.

Peripartal heart disease. Heart disease may first manifest in the peripartum period. This is probably a heterogeneous group.

Certain toxins have their main impact on the endomyocardium such as in carcinoid heart disease and methysergide which also affect valves.

Certain heredofamilial disorders such as Noonan's syndrome and lentiginosis may cause a disorder indistinguishable from hypertrophic cardiomyopathy, and Friedreich's ataxia may cause asymmetric hypertrophy with or without dilatation.

Certain disorders do not lend themselves readily to these groups and are listed as "Unclassified". Examples are endocardial fibroelastosis, the infantile form of cardiomyopathy, with histiocytoid change and "Fiedler's myocarditis".

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The floppy mitral valve
Study on pathogenesis

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SUMMARY The pathogenesis of the floppy valve syndrome is not fully solved. An almost invariable histological finding is the great accumulation of mucinous material in the valve leaflets and constitutes the basis of the valvular theory of the syndrome. The presence of a mucinous layer in normal valves—the zona spongiosa—is not well recognised. To establish the normal range of the extent of this zone, 50 excised mitral valves from patients aged 2 to 89 years and who died as a result of road traffic accidents or non-cardiac causes have been analysed by measuring the thickness of the zone in relation to the valve thickness. A range of 0 to 60 per cent was found and this was not influenced by age.

The findings were compared with 50 patients clinically diagnosed as suffering from the floppy valve syndrome. A value of over 60 per cent (range 62 to 94%) was found in 43 patients. The increase in the extent of the mucinous material was considered to be a secondary change in the thickened fibrosa which normally accompanies the floppy valve syndrome. Measurements of zona spongiosa falling within the normal range were found in seven patients. The clinical features, complications, and accompanying conditions have also been analysed. Chordal rupture had occurred in 20 patients, infective endocarditis in three, and calcification was found in four valves. In four patients the aortic valve was also involved and accompanying aortic root dilatation in an additional patient. It is suggested that these patients should not be included in the group of Marfan's *forme fruste,* nor in the typical floppy mitral valve syndrome.

Apart from the valvular theory, the myocardial theory in the pathogenesis of the syndrome has been discussed and the components ensuring normal mitral valve function have been reviewed.

It is concluded that an inherent, prominent zona spongiosa predisposes to the floppy valve syndrome, particularly if any one of the components of normal valve function is abnormal.

For the past 15 years attention has focused on the floppy valve syndrome, first described by Fernex and Fernex[1] in 1958. It is characterised by protrusion particularly of the posterior valve leaflet into the left atrium and results in recognisable signs[2–5] constituting a specific syndrome.[6] Other synonyms for the syndrome include prolapse of the mitral valve,[7] billowing of the mitral valve,[3] and ballooning, or the syndrome of mid-late systolic click and late systolic murmur.[8]

Despite many possible suggestions, the pathogenesis of the floppy valve syndrome is still not fully understood. Mitral regurgitation can occur as the result of failure of any of several anatomical components which interact to ensure normal functional integrity of the mitral valve apparatus[9] but must be distinguished from the syndrome. Dilatation of the valve ring has been established in the floppy valve syndrome[10] and more recently attention has been drawn to normal variants in the deposition of chordae tendineae.[11] Myocardial and haemodynamic alterations, as well as anatomical variations of the circumflex branch of the left coronary artery, have also been suggested as resulting in the syndrome.

There is a considerable body of opinion suggesting that myxomatous degeneration is the underlying mechanism of mitral valve prolapse.[12 13] In many reports dealing with histological changes, definition of specific location of myxomatous change and "fibrosis" has been omitted.[14] The normal structure of valve leaflets[15] has also not been taken into account and it is the purpose of this study to investigate the variable prominence of the zona spongiosa—a constant component of normal valve

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leaflets—and to compare the findings with those valves removed at surgical operation from patients firmly diagnosed as suffering from the floppy valve syndrome.

Material and methods

NORMAL VALVES

Valves removed at necropsy—21 female and 29 male, 2 to 89 years of age—of patients who died as a result of road traffic accidents, or from extracardiac causes, have been available for study. Tissue from the centre of the "scallops" and from the region of strutt chordae[16] was selected from the patient's posterior leaflet, as were samples from the anterior leaflet near the posteromedial commissure of the leaflet. The blocks were paraffin embedded and processed in the conventional manner.

For histological examination five μm thick sections were stained with haematoxylin and eosin and Weigert's elastic van Gieson stain. Histochemical examination included staining with periodic acid Schiff, colloidal iron, toluidine blue at pH 3 and pH 5, and Congo red stains.[17] These investigations were carried out on isolated specimens. Staining with Alcian blue at pH 2·5 was carried out on every block selected.

Isolated specimens were also selected for electron microscopical examination. This material was placed in buffered 3 per cent glutaraldehyde for one hour at 4°C. Subsequently the fixing fluid was replaced by buffered sucrose washing solution (4°C) pH 7·4. Post-fixation in 1 per cent osmium tetroxide was undertaken and the tissue was embedded in epon. Fifty nm thick sections were cut with a Porter Blum MT 1 ultramicrotome and stained with uranyl acetate and lead citrate and viewed on a Phillips 301 electron microscope.

ASSESSMENT OF ZONA SPONGIOSA

Measurement of the thickness of the zona was undertaken on the Alcian blue stained preparation, in the middle third of the valve leaflet (base to free edge), using an eye piece graticule. The thickness

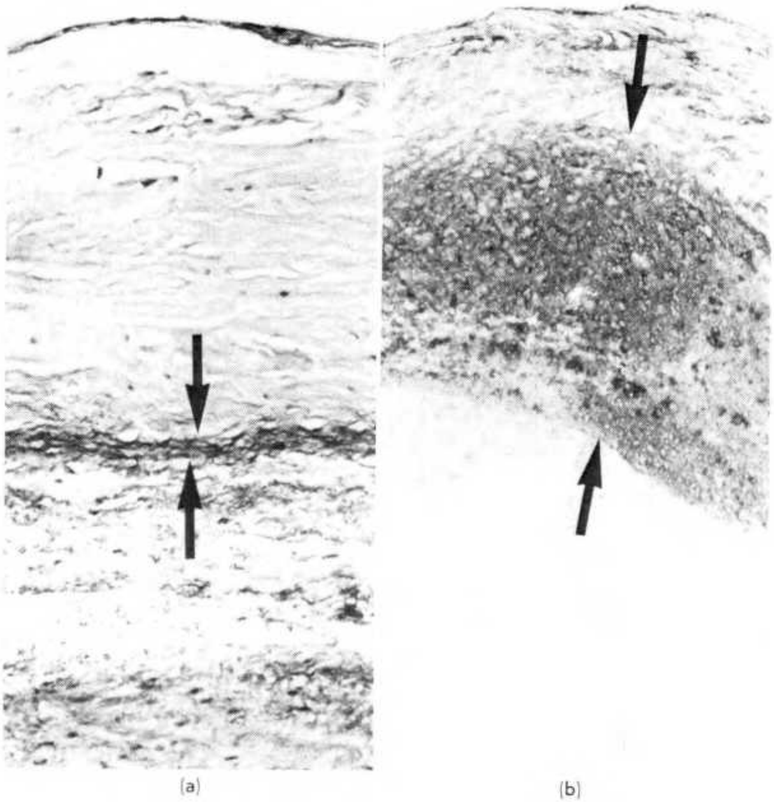
(a) (b)

Fig. 1 (a) *Photomicrograph of a normal posterior leaflet of the mitral valve, showing a thin zona spongiosa (3%). (Alcian Blue, original magnification × 80.)* (b) *Posterior leaflet of the normal mitral valve with a prominent zona spongiosa (47·6%). The extent of the thickness of the valve leaflet can just be discerned. (Alcian Blue, original magnification × 80.)*

of the zona was expressed as a percentage of the width of the valve leaflet.

FLOPPY MITRAL VALVES

Mitral valves from 50 patients—34 male and 16 female, removed at operation (age range 6 to 70 years)—were processed and measured in exactly the same manner as the tissue from the normal subjects. Other histochemical analyses and electron microscopy were carried out in isolated instances.

Table 1 *Variation of normal zona spongiosa*

Age (y)	*No. of valves*	*Zona spongiosa*	
		From (%)	*To* (%)
0–10	5	0	48·4
11–20	2	10·2	33·6
21–30	3	25·3	50·4
31–40	5	23·2	35·7
41–50	7	0	50·3
51–60	7	8·3	28·2
61–70	9	18·1	60·0
71–80	10	0	13·3
81–90	2	12·3	23·6

Results

NORMAL VALVES

Microscopical changes

No differences between male and female cases were noted. In Table 1 the cases are grouped according to age in decades and the number of valves available for each group are listed. The range of the zona spongiosa, expressed as a percentage of the valve thickness for each group, is detailed. The extreme variability of the prominence of this valvar component is striking. In some cases the zona was represented by a single cell thick streak of Alcian blue positive material (0%), while in others it occupied 60 per cent of valve thickness. Fig. 1a and 1b illustrate a small and prominent zona spongiosa.

Histochemical analysis

This showed a strongly positive reaction to periodic acid Schiff staining, minimally affected by diastase digestion. A strongly positive reaction was also obtained by colloidal iron ablated after testicular hyaluronidase digestion. Faint metachromasia was obtained with toludine blue staining at pH 3. The Congo red treated tissue showed only very faint

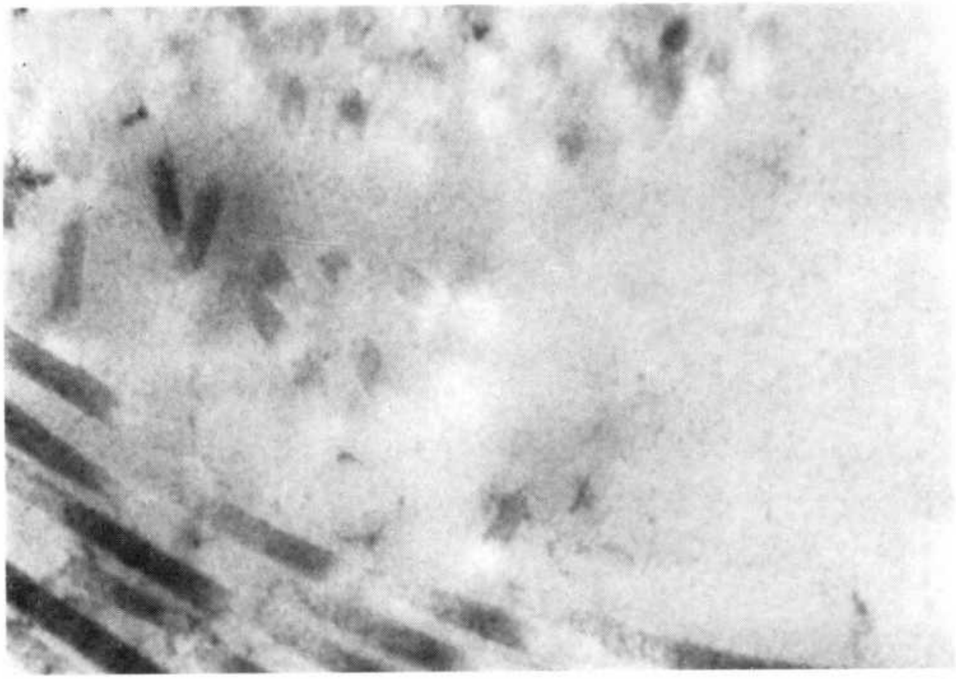

Fig. 2 *Electron micrograph of the zona spongiosa in a normal valve leaflet, showing amorphous material. The adjacent collagen fibrils show normal periodicity. (Lead citrate and Uranyl acetate, original magnification × 147 500.)*

apple green fluorescence on examination under crossed polaroids.

Electron microscopical changes of the area of the zona spongiosa consisted of amorphous material surrounded by collagen fibrils showing the typical periodicity (Fig. 2).

FLOPPY MITRAL VALVES

Macroscopical examination of these valves showed characteristic features consisting of doming towards the left atrium, principally of the posterior mitral valve leaflets from side to side, and from the free edge of the basal attachment. In 23 out of 50 patients the anterior mitral valve leaflets were also significantly affected. In three patients that leaflet showed the most severe change and in one patient the anterior leaflet alone was affected (case 11, Table 2). Doming was most prominent between chordal insertions and in the middle third of the valve leaflet. These leaflets were usually thin, transparent, and showed a bluish tinge. Along the line of closure in all valves, but also in the region of the clear zone, in several cases thickening was present, altering the appearance to white and opaque. The commissures were widely separated and measurements exceeded the normal range of linear measurement of 90 to 110 mm by up to 20 mm. In four patients the measurements exceeded 160 mm (dilated valve ring, Table 2). Elongation of the chordae was frequently found and could be accurately assessed when the specimen included attached tips of papillary muscles. Beading of the chordae was a characteristic and frequent finding. In cases of rupture the chordae tapered to a fine point (Fig. 3). The salient features of the macroscopical involvement are listed in Table 2. This table has been arranged according to age. The sex of the patient and the time when a murmur was first heard are also stated. Complications and associated or other conditions are included. In 20 patients rupture of chordae tendineae was found. Evidence of infective endocarditis was observed in three patients. In two patients atrial septal defect was diagnosed and patency of the fossa ovalis was found in another two patients. Calcification was found in four valves examined.

Measurements of the zona spongiosa in Table 2 have been confined to the posterior mitral valve leaflets. In those valves where the anterior mitral valve leaflet showed microscopical dominant features, the posterior leaflet showed similar or more severe histological changes. In 43 cases over 60 per cent of the valve leaflet was occupied by the zona spongiosa. In the remaining seven valves the extent of the zona spongiosa fell within the range observed in normal valves.

Apart from the prominent zona spongiosa and the increased "length" of the posterior mitral valve

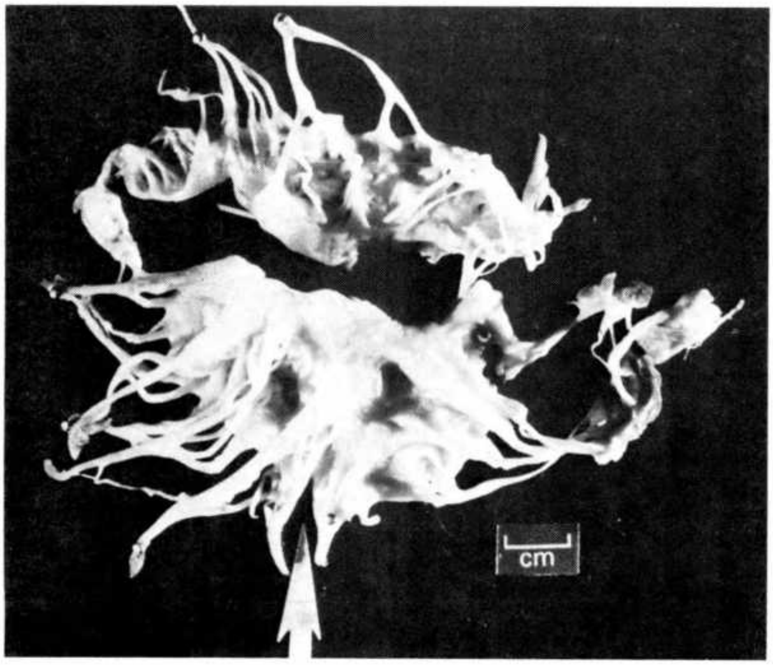

Fig. 3 *A specimen of a surgically removed mitral valve (ventricular aspect) from a patient with the floppy valve syndrome and rupture of chordae tendineae. The arrow indicates the larger anterior leaflet.*

Table 2 *Clinical data, macroscopical involvement of valves, complications, and measurements of zona spongiosa (post. leaflet) of patients with floppy valve syndrome*

No.	*Age (y)*	*Sex*	*History of murmur*	*Gross appearance of mitral valve involvement*	*Other valves*	*Complications*	*Associated condition and other diseases*	*Zona spongiosa* (%)
1	6	M	3 mth	Both leaflets	—	—	—	74·7
2	9	M	5 mth	Both leaflets	—	—	—	65·2
3	14	M	14 y	Both leaflets	—	—	—	66·6
4	17	M	4 y	Posterior leaflet	—	—	—	90·6
5	18	M	25 d	Both leaflets	—	—	Atrial septal defect	94·0
6	27	M	6 mth	Posterior leaflet	—	Calcification	—	87·5
7	44	M	19 y	Both leaflets	—	Ruptured chordae	—	60·0
8	44	F	6 y	Both leaflets	—	—	—	46·4
9	45	F	15 y	Posterior leaflet	Aortic valve	—	—	90·0
10	45	F	28 y	Both leaflets	Aortic valve	—	—	66·6
11	50	M	27 y	Anterior leaflet	—	Ruptured chordae	—	85·7
12	50	M	14 y	Both leaflets	—	—	—	64·4
13	51	M	1 y	Predominantly anterior leaflet	—	—	Patent foramen ovale	52·6
14	52	M	44 y	Posterior leaflet	—	—	Dilated valve ring	64·2
15	52	M	8 y	Posterior leaflet	Aortic valve and root dilatation	—	Dilated valve ring	85·7
16	52	M	8 y	Both leaflets	—	—	—	87·8
17	53	F	10 y	Posterior leaflet	—	—	—	91·0
18	54	M	1 y	Both leaflets	Aortic valve	—	—	78·0
19	54	M	8 y	Both leaflets	—	Calcification	—	62·3
20	55	F	1 mth	Predominantly anterior leaflet	—	—	Ischaemic heart disease	87·8
21	55	M	8 y	Both leaflets	—	—	Dilated valve ring	72·1
22	55	M	8 y	Both leaflets	—	—	Ischaemic heart disease	82·9
23	56	M	7 y	Posterior leaflet	Aortic valve	Ruptured chordae	—	47·1
24	57	M	34 y	Posterior leaflet	—	—	—	68·0
25	57	F	1 mth	Both leaflets	—	—	—	54·1
26	58	M	10 y	Posterior leaflet	—	Ruptured chordae	—	89·5
27	58	F	Many years	Both leaflets	—	Ruptured chordae	Calcification of annulus	75·5
28	59	M	4 mth	Predominantly anterior leaflet	—	—	—	85·0
29	59	F	28 y	Both leaflets	—	—	—	74·0
30	59	M	2 y	Both leaflets	—	Ruptured chordae	—	65·2
31	60	F	10 y	Both leaflets	—	Calcification	—	66·6
32	60	F	5 y	Posterior leaflet	—	Ruptured chordae	—	68·7
33	61	M	4 y	Posterior leaflet	—	—	—	67·6
34	62	M	29 y	Posterior leaflet	—	Ruptured chordae	Patent foramen ovale	60·0
35	62	M	2 mth	Posterior leaflet	—	Ruptured chordae	Ischaemic heart disease	74·1
36	63	M	8 y	Posterior leaflet	—	Ruptured chordae	—	76·2
37	63	M	2·5 y	Both leaflets	—	Ruptured chordae	Atrial septal defect	76·9
38	64	M	26 y	Posterior leaflet	—	Ruptured chordae	—	70·0
39	64	M	31 y	Both leaflets	—	Ruptured chordae	—	83·3
40	64	M	49 y	Both leaflets	—	Infective endocarditis	—	87·8
41	64	M	8 y	Posterior leaflet	—	Ruptured chordae	Ischaemic heart disease	66·6
42	65	M	22 y	Both leaflets	—	Infective endocarditis	—	74·0
43	65	M	4 y	Posterior leaflet	—	Ruptured chordae	—	85·0
44	67	F	5 y	Both leaflets	—	Ruptured chordae	Dilated valve ring	89·0
45	69	F	13 y	Posterior leaflet	—	Ruptured chordae, infective endocarditis	—	84·2
46	69	F	5 y	Posterior leaflet	—	Calcification	—	68·0
47	69	F	14 y	Posterior leaflet	—	Ruptured chordae,	—	58·3
48	70	M	22 y	Posterior leaflet	—	—	Ischaemic heart disease	69·2
49	70	F	8 y	Posterior leaflet	—	Ruptured chordae	—	87·5
50	70	F	8 y	Posterior leaflet	—	Ruptured chordae	—	70·0

leaflet, the histological appearances did not differ from those observed in the normal valve tissue. The architecture was preserved and vascularity was not increased. Superimposition of predominantly collagen tissue on the line of closure, and along the atrial aspect of the valve leaflets, indicated that regurgitation had been present for some time (Fig. 4). The myxomatous tissue extended into the chordae tendineae and was particularly prominent in the areas noted as beading macroscopically. Thickening of the chordae by superimposition of collagen tissue was also found.

Histochemical analyses did not differ from those of the normal valves.

Electron microscopical examination showed similar amorphous material to that observed in normal valves, but the collagen tissue surrounding these areas frequently showed loss of periodicity of collagen fibrils.

Discussion

For assessment of the extent of the myxomatous zone occupied in the valve leaflets, the middle third (free edge to basal attachment) was chosen because of frequent thickening and often even more prominent myxomatous tissue being present in the area of the line of closure in the diseased valves. Though invariably some diffuseness of the adjacent collagen tissue was found, examination at low magnification showed a fairly clear separation between myxomatous tissue and the adjacent unaffected collagen.

Histochemical examination confirmed the changes previously reported,[17] suggesting that the mucinous area was predominantly composed of uronic acid mucopolysaccharides. A similar conclusion was reached by Torii *et al.*,[18] by determining the carbazol/orcinol ratio of uronic acid in acid mucopolysaccharides. Apple green fluorescence by examination under crossed polaroids, after staining with Congo red, was only very faint in our study though a somewhat stronger reaction has been noted.[17]

Electron microscopical changes only showed evidence of degeneration of the adjacent collagen fibrils, having resulted in loss of periodicity. In all other respect no differences between affected and normal valves could be identified.

The normal function of the mitral valve apparatus is dependent on six components: the left atrial wall; the annulus; valve leaflets; chordae tendineae; papillary muscles and left ventricular wall.[9] Abnormalities of any of these components—such as deficiency or excess of valvar tissue, abnormally long or short chordae, papillary muscle dysfunction, and alteration of the left ventricular shape—

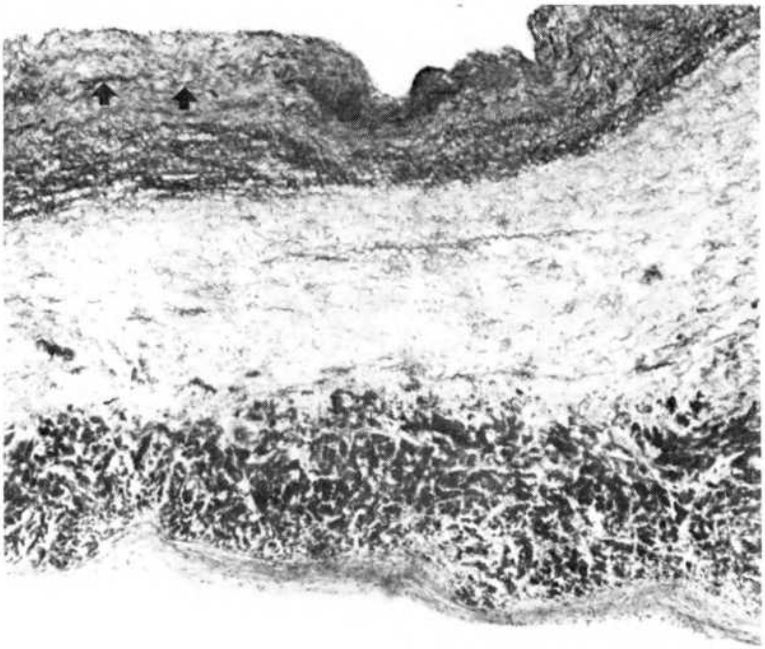

Fig. 4 *Photomicrograph of the posterior mitral valve leaflet from a patient with the floppy valve syndrome. Superimposition of predominantly collagen tissue on the "auricularis" is present (arrowed) indicating valvular regurgitation. The pale central area is the zona spongiosa. (Weigert's elastic van Gieson, original magnification × 80.)*

can result in abnormal mitral valve function. Distinction must be made, however, between abnormal closure, for example resulting from papillary muscle dysfunction, and true mitral valve prolapse. In the syndrome characteristic doming towards the left atrium and elongation of the chordae tendineae (often showing beading) are found, together with expansion of the valve area. Nevertheless, dilatation of the mitral valve annulus of sufficient severity, so as to cause mitral regurgitation, has been established in patients with the floppy valve syndrome.[10] In the present study measurement of the excised valves exceeded 160 mm in four of the 50 cases, confirming that annular dilatation can significantly contribute to regurgitation. In all other cases some increase was found above the normal range of mitral valve dimensions (normal: 90 to 110 mm), most probably from dilatation subsequent to mitral regurgitation.

The aetiology of the "floppy valve syndrome" is not solved but two major theories have been suggested: the valvular and the myocardial.[6] The former suggestion explains the clinical manifestations, chest pain being caused by excessive stretching of the papillary muscles.[19 20] Sudden tensing of the everted valve leaflets is responsible for the characteristic click.[21] The mid-late systolic murmur is attributed to increasing regurgitation of valve leaflets as prolapse develops.[21 22]

The other major theory, the myocardial theory, has included a variety of angiographic and haemodynamic findings such as abnormal protrusion of the inferior aspect of the left ventricle[23] and non-contraction or late systolic expansion of the inflow tract of the left ventricle.[24] Absence of the atrioventricular groove branch of the circumflex of the left coronary artery has been the suggested explanation for segmental myocardial dysfunction[25]; its absence is frequently compensated by a large posterolateral branch of the right coronary artery.[24] Left ventricular asynergy[26 27] and haemodynamic disturbance—such as a constrictive pattern[20] and an increase in left ventricular end-diastolic pressure, low resting cardiac index, or an inappropriate rise during exercise[27]—concludes the myogenic cardiac theory. To explain the various changes, an underlying cardiomyopathy has also been suggested.[27] The association of the "floppy valve syndrome" with coronary arterial disease, resulting in papillary muscle involvement (dysfunction), has been suggested.[28 29]

Although in the present study five patients had clinical manifestations of ischaemic heart disease and mitral regurgitation, which may occur in association with papillary muscle dysfunction, we agree with Jeresaty and Liss[10 28 29] that this combination is likely to be coincidental in the "floppy valve syndrome". An incidence of only 2 to 3 per cent of coronary arterial disease has been shown to exist in these patients by selective coronary arteriography.[6]

The anatomy of the normal mitral valve has been meticulously studied.[16 31] Variation in the chordal arrangement and atypical chordae were encountered in 37 of the 50 hearts examined. In a more recent study[11] abnormalities were noted in the deposition of chordae tendineae in 36 out of 40 valves obtained from patients with prolapse, particularly those inserting into the commisural area and rough zone areas and preferentially involving the posteromedial commissural area and the middle scallop of the posterior leaflet. Associated finger-like papillary muscle, single long chordae, or haphazard arrangement were encountered, resulting in insufficient valvar support. Weakness of the central area of the valve leaflet was found to be an essential lesion.[32]

Our findings at macroscopical examination confirm the presence of the severest doming around the posteromedial commissure, with involvement of the middle scallop of the posterior leaflet. When the anterior leaflet was involved, the area adjacent to the commissure showed the severest changes. In severely affected valves the entire posterior leaflet, and not infrequently the anterior leaflet, showed evidence of doming. Similar findings have been reported.[11 32]

Regarding complications and associated conditions in our series, 20 of the 50 patients suffered rupture of the chordae tendineae close to a point where secondary fibrous thickening and myxomatous tissue were prominent. Early surgical intervention was achieved. In three patients morphological evidence of infective endocarditis was present; in two patients an atrial septal defect in the region of the fossa ovalis was found (secundum type) and in another two probe patency of the fossa ovalis was noted. A 5 per cent incidence of atrial septal defect has been reported.[6]

Returning once more to the valvar theory, histologically, myxomatous degeneration has consistently been documented.[33–36] With the exception of three contributions,[14 37 38] the normal histological structure has either not been mentioned or not taken into account and has led to the suggestion that the process of degeneration of the fibrosa is present.[39]

As early as 1931, Gross and Kugel[15] described the normal histology in detail. Between the auricularis (a thin layer composed of collagen and elastic tissue covering the atrial aspect of valve leaflet) and the fibrosa (a thick layer composed of collagen tissue which affords the main support of the valve) is the zona spongiosa. This present study is the first account of measurement of this structure. The results have shown that variability is great, ranging from just a cell thick streak, expressed as 0 per cent, to occupying 60 per cent of the thickness of the valve leaflet. The extent is not affected by increasing age. By contrast, 43 of the 50 valves removed surgically for prolapse from patients showed values above 60 per cent (range 62 to 94%). In seven valves examined the measurement of the extent of the zona fell within the range encountered in the normal subjects. Nevertheless, clinical and macroscopical findings typical of the "floppy valve syndrome" were present in the tissue. This finding emphasises that though myxomatous tissue is consistently present in "floppy valves", histological examination alone may overdiagnose the condition. It further emphasises the fact that other mechanisms, such as abnormal chordal arrangement, may play a role culminating in the clinically recognisable syndrome.

As a result of our study we suggest that an individual is born either with a thin or a thick zona spongiosa. Family studies[40–42] support such a suggestion. Those patients with a prominent zona, inherently weakening the valve, are liable to develop the syndrome, particularly if one or the other factor discussed above is additionally present.

Degeneration of the fibrosa may occur to some extent but in view of the values of up to 60 per cent found in normal valves, it seems reasonable to suggest that only minor, secondary degeneration is necessary to account for the higher values obtained in abnormal valves. It is likely that this secondary degeneration is caused by lysis, which can occur in the accompanying thickening of the fibrosa. Support for such a supposition is provided by examining valves in patients with acquired heart disease, such as rheumatic fever. Towards the free margin of these valves extensive thickening is usually present in which an excess of myxomatous tissue is often found. Elsewhere in the valves the zona is frequently not conspicuous. This prominence of myxomatous tissue in the distal portion of the valves may have led to difficulty in distinguishing the two conditions.[43] Other changes usually make distinction easy. In the floppy valve the architecture is preserved and no increase in vascularity is evident. Thickening, when present, consists of a well-defined layer of predominantly collagen tissue superimposed on the surface of the auricularis. Thickening of the fibrosa is frequently present. In valves affected by the rheumatic process, severe thickening, distortion or destruction of the normal architecture, increased vascularity and calcification, together with a variable chronic inflammatory infiltrate, are found.

Calcification of the floppy valve may occur,[14] though this is rare. It was found in four cases in our series.

Changes similar to those described for the mitral valve have been observed in the aortic valve in four patients and in one additional patient aortic valvar changes were accompanied by dilatation of the aortic root. Accompanying aortic valve involvement is well recognised,[44 45] and the question arises whether the combination of aortic and mitral valve changes constitutes a *forme fruste* of Marfan's disease. Indeed it has been suggested that isolated floppy mitral valve could be considered a form of this disease. This concept is supported to some extent by a report on three patients who developed dissecting aneurysms of the aorta after clamping of the aorta during operation for mitral valve replacement.[46] Despite the overlapping features there is, however, no firm evidence that isolated mitral valve prolapse forms part of the spectrum of Marfan's disease. When the aortic valve is affected as well, it should also not be classified under Marfan's disease or typical mitral valve prolapse.[47]

We conclude that an inherent prominent zona spongiosa, in otherwise normal valves, predisposes to the floppy valve syndrome. Once doming has taken place, secondary thickening of the valve leaflet occurs, with extension of the myxomatous tissue into the fibrosa. Functional or anatomical abnormalities of any components, ensuring normal mitral valve function, are important contributory factors in the development of this syndrome, particularly in cases with less prominent zona spongiosa.

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References

1 Fernex M, Fernex C. La dégénérescence mucoide des valvules mitrales; ses répercussions fonctionnelles. *Helv Med Acta* 1958; **25**: 694–705.

2 Barlow JB, Pocock WA, Marchand P, Denny M. The significance of late systolic murmurs. *Am Heart J* 1963; **66**: 443–52.

3 Barlow JB, Bosman CK, Pocock WA, Marchand P. Late systolic murmurs and non-ejection ("mid-late") systolic clicks: an analysis of 90 patients. *Br Heart J* 1968; **30**: 203–18.

4 Barlow JB, Pocock WA. The problem of non-ejection systolic clicks and associated mitral systolic murmurs: emphasis on the billowing mitral leaflet syndrome. *Am Heart J* 1975; **90**: 636–55.

5 Barlow JB, Pocock WA. Mitral valve prolapse, the specific billowing mitral leaflet syndrome, or an

insignificant non-ejection systolic click. *Am Heart J* 1979; **97:** 277–85.

6 Jeresaty RM. Etiology of the mitral valve-prolapse-click syndrome (Editorial). *Am J Cardiol* 1975; **36:** 110–3.

7 O'Rourke RA, Crawford MH, Johnson AD, Davidson RM, LeWinter MM, Karliner JS. Prolapsing mitral valve leaflet syndrome. *West J Med* 1975; **122:** 217–31.

8 Shell WE, Walton JA, Clifford ME, Willis PW. The familial occurrence of the syndrome of mid-late systolic click and late systolic murmur. *Circulation* 1969; **39:** 327–37.

9 Perloff JK, Roberts WC. The mitral valve apparatus. Functional anatomy of mitral regurgitation. *Circulation* 1972; **46:** 227–39.

10 Bulkley BH, Roberts WC. Dilatation of the mitral anulus. A rare cause of mitral regurgitation. *Am J Med* 1975; **59:** 457–63.

11 Becker AE, DeWit APM. Mitral valve apparatus. A spectrum of normality relevant to mitral valve prolapse. *Br Heart J* 1979; **42:** 680–9.

12 Jeresaty RM, Liss JP. Midsystolic clicks and coronary heart disease. *Chest* 1973; **63:** 297–8.

13 Bittar N, Sosa JA. The billowing mitral valve leaflet; report on fourteen patients. *Circulation* 1968; **38:** 763–70.

14 Guthrie RB, Edwards JE. Pathology of the myxomatous mitral valve. Nature, secondary changes and complications. *Minn Med* 1976; **59:** 637–47.

15 Gross L, Kugel MA. Topographic anatomy and histology of the valves in the human heart. *Am J Pathol* 1931; **7:** 445–74.

16 Ranganathan N, Lam JHC, Wigle ED, Silver MD. Morphology of the human mitral valve. II. The valve leaflets. *Circulation* 1970; **41:** 459–67.

17 Marshall CE, Shappell SD. Sudden death and the ballooning posterior leaflet syndrome. *Arch Pathol* 1974; **98:** 134–8.

18 Torii S, Nakao K, Angrist AA. Acid mucopolysaccharide in heart valves (letter). *Lancet* 1965; **ii:** 1186–7.

19 Hancock EW, Cohn K. The syndrome associated with midsystolic click and late systolic murmur. *Am J Med* 1966; **41:** 183–96.

20 Jeresaty RM. The syndrome associated with midsystolic click and /or late systolic murmur; analysis of 32 cases. *Chest* 1971; **59:** 643–7.

21 Criley JM, Lewis KB, Humphries JO, Ross RS. Prolapse of the mitral valve: clinical and cineangiocardiographic findings. *Br Heart J* 1966; **28:** 488–96.

22 Tavel ME, Campbell RW, Zimmer JF. Late systolic murmurs and mitral regurgitation. *Am J Cardiol* 1965; **15:** 719–25.

23 Grossman H, Fleming RJ, Engle MA, Levin AH, Ehlers KH. Angiocardiography in the apical systolic click syndrome; left ventricular abnormality, mitral insufficiency, late systolic murmur and inversion of T waves. *Radiology* 1968; **91:** 898–904.

24 Liedtke AJ, Gault JH, Leaman DM, Blumenthal MS. Geometry of left ventricular contraction in the systolic click syndrome. Characterisation of a segmental myocardial abnormality. *Circulation* 1973; **47:** 27–35.

25 Gentzler RD, Gault JH, Hunter AS, Liedtke AJ. Congenital absence of the left circumflex coronary artery (LCCA) in the systolic click syndrome (SCS) (abstract). *Circulation* 1973; **47,** suppl IV: 65.

26 Gooch AS, Vicencio F, Maranhao V, Goldberg H. Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome. *Am J Cardiol* 1972; **29:** 611–20.

27 Gulotta SJ, Gulco L, Padmanabhan V, Miller S. The syndrome of systolic click, murmur, and mitral valve prolapse—a cardiomyopathy? *Circulation* 1974; **49:** 717–28.

28 Steelman RB, White RS, Hill JC, Nagle JP, Cheitlin MD. Midsystolic clicks in arteriosclerotic heart disease; a new facet in the clinical syndrome of papillary muscle dysfunction. *Circulation* 1971; **44:** 503–15.

29 Cheng TO. Late systolic murmur in coronary artery disease. *Chest* 1972; **61:** 346–56.

30 Jeresaty RM, Liss JP. Midsystolic clicks in arteriosclerotic heart disease. *Circulation* 1972; **45:** 1145–6.

31 Lam JHC, Ranganathan N, Wigle ED, Silver MD. Morphology of the human mitral valve. I. Chordae tendineae: a new classification. *Circulation* 1970; **41:** 449–58.

32 Davies MJ, Moore BP, Braimbridge MV. The floppy valve. Study of incidence, pathology, and complications in surgical, necropsy, and forensic material. *Br Heart J* 1978; **40:** 468–81.

33 Cohn LH, Hultgren HN, Angell WW, Grehl TM, Kosek JC. Prolapsing mitral valve with mucinous degeneration. *Calif Med* 1973; **118:** 43–7.

34 McCarthy LJ, Wolf PL. Mucoid degeneration of heart valves. "Blue valve syndrome." *Am J Clin Pathol* 1970; **54:** 852–6.

35 Trent JK, Adelman AG, Wigle ED, Silver MD. Morphology of a prolapsed posterior mitral valve leaflet. *Am Heart J* 1970; **79:** 539–43.

36 Ranganathan N, Silver MD, Robinson TI, *et al.* Angiographic-morphologic correlation in patients with severe mitral regurgitation due to prolapse of the posterior mitral valve leaflet. *Circulation* 1973; **48:** 514–8.

37 Joseph S, Emanuel R, Sturridge M, Olsen E. Congenital aortic valve disease with rupture of mitral chordae tendineae. *Br Heart J* 1976; **38:** 665–73.

38 Aslam PA, Eastridge CE, Bernhardt H, Pate JW. Myxomatous degeneration of cardiac valves. *Chest* 1970; **57:** 535–9.

39 Devereux RB. Mitral valve prolapse. *Am J Med* 1979; **67:** 729–31.

40 Hunt D, Sloman G. Prolapse of the posterior leaflet of the mitral valve occurring in eleven members of a family. *Am Heart J* 1969; **78:** 149–53.

41 Standard M, Sloman JG, Hare WS, Goble AJ. Prolapse of the posterior leaflet of the mitral valve: a clinical familial, and cineangiographic study. *Br Med J* 1967; **3:** 71–4.

42 Linhart JW, Taylor WJ. The late apical systolic murmur. *Am J Cardiol* 1966; **18:** 164–8.

43 Davis RH, Schuster B, Knoebel SB, Fisch C. Myxomatous degeneration of the mitral valve. *Am J Cardiol* 1971; **28:** 449–55.

44 O'Brien KP, Hitchcock GC, Barratt-Boyes BG, Lowe JB. Spontaneous aortic cusp rupture associated with valvular myxomatous transformation. *Circulation* 1968; **37:** 273–8.

45 Estevez, CM, Dillon JC, Walker PD, Feigenbaum H, Chang S. Echocardiographic manifestations of aortic cusp rupture in a myxomatous aortic valve. *Chest* 1976; **69:** 685–7.

46 McKay R, Yacoub MH. Clinical and pathological findings in patients with "floppy" valves treated surgically. *Circulation* 1973; **48,** suppl. III: 63.

47 Devereux RB, Perloff JK, Reichek N, Josephson ME. Mitral valve prolapse. *Circulation* 1976; **54:** 3–14.

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Br Heart J 1980; **44:** 684–91

Sick sinus syndrome in childhood

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SUMMARY The clinical and electrocardiographic findings in five children with the sick sinus syndrome and an otherwise normal heart are described. There were three boys and two girls. Their age at onset of either bradycardia or symptoms ranged from 1 day to 7 years. In one patient, the youngest ever reported with this syndrome, bradycardia was noted before birth. Four children presented with neurological symptoms—attacks of dizziness, fainting spells, or syncope. One boy, treated for epilepsy before the underlying arrhythmia was diagnosed, died suddenly while playing. One child had near-fatal syncope caused by ventricular tachycardia. Continuous 24-hour electrocardiographic monitoring is the best method of assessing the severity of the condition. Sinus bradycardia, sinuatrial block, and periods of sinus arrest up to 4·8 seconds were recorded. Two patients had associated atrioventricular block and were therefore presumed to have binodal disease. Atrial fibrillation or flutter occurred in three patients. Isolated sick sinus syndrome may be a life-threatening condition in childhood for which, in selected cases, the insertion of a permanent pacemaker is indicated.

Most reports on the sick sinus syndrome deal exclusively with adults or the elderly[1–4]; in childhood the condition is rare. It has been reported to occur after intra-atrial operations with injury to the sinuatrial node or its blood supply, particularly after the Mustard operation[5–7] and also in children with various congenital cardiac malformations,[8–10] but occasionally it occurs in children and adolescents with no other evidence of heart disease.[10 11] The latter condition, which is probably of congenital origin, is not sufficiently recognised for a number of reasons. The presenting symptoms, produced by intermittent cerebral ischaemia, usually mimic central nervous disorders. With the exception of bradycardia, which is often intermittent, there is frequently no abnormality on physical examination and routine electrocardiograms. Finally, the syndrome is generally considered to occur only in adults. Its diagnosis in children, however, is important, for the arrhythmia may threaten life and need specific treatment.

In this study, five children with the sick sinus syndrome are presented. The wide range and variability of symptoms and the value of continuous electrocardiographic monitoring in diagnosis are emphasised.

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Patients and methods

Between January 1967 and January 1979, five children with severe bradycardia were seen. None had clinical evidence of structural heart disease. Only one, being treated for epilepsy, was taking drugs. All had routine electrocardiograms taken and, four, continuous 24-hour electrocardiographic tape recordings. Each patient met at least two of the following three criteria: (1) long periods of bradycardia, defined as a heart rate of 40 beats/min or less lasting one minute or more, (2) episodes of sinus arrest of three seconds or longer, (3) episodes of 2:1 or 3:1 sinuatrial block. There were three boys and two girls. Their ages, at the onset of bradycardia or symptoms, ranged from 1 day to 7 years (Table 1).

For 24-hour monitoring a two-channel Medilog tape recorder with build-in reference time signal (Oxford Medical Instruments) was used. Recordings were played back on a semiautomatic high-speed analyser, giving a visual display of the heart rhythm on a 40 seconds memory oscilloscope. Arrhythmias were analysed on direct write-out traces. The children over 6 years of age had an exercise test on a bicycle ergometer. The younger children were asked to run a distance of 150 metres. Electrophysiological studies were performed in three

Table 1 *Clinical data in five children with isolated sick sinus syndrome*

Case No.	*Age at onset of symptoms (y)*	*Age at which bradycardia first noted (y)*	*Symptoms*	*Treatment*
1	5	8	Epileptic fits, died suddenly aged 10	None
2	7	7	Syncope, dizziness	Isoprenaline, anticoagulants
3	5	4	First syncope near-fatal	Permanent pacemaker
4	—	1 day	None	Permanent pacemaker
5	6	12	Syncope	Isoprenaline

children. His bundle recordings were obtained by the method of Scherlag *et al.*[12] Sinus recovery times were recorded after high atrial pacing for three minutes. For programmed electrical stimulation the JSI-stimulator (Janssen Scientific Instruments) was used. In two patients, studied after the implantation of a permanent cardiac pacemaker, the underlying escape rhythm was assessed by inhibition of the pacemaker using chest wall stimuli produced by a Grass stimulator with variable impulse duration and voltage.

Case reports

The salient clinical and electrocardiographic features are summarised in Tables 1, 2, and 3. In view of the scarcity of similar published reports and the wide spectrum of symptoms, the case histories will be presented in detail.

Table 2 *Electrocardiographic findings on routine and 24-hour electrocardiograms*

Case No.	*Age (y)*	*Slowest heart rate (beats/min)*	*Sinuatrial block*	*Longest asystole (s)*
1	8	40	Sinus arrest	1·5
2	12	24	2:1 and 3:1	4·2
3	4	22	3:1	3·5
4	4	30	2:1	4·8
5	12	32	2:1	2

CASE 1

A 5-year-old boy began to have short attacks of syncope which were thought to be epilepsy and were treated with diphenylhydantoin. In July 1967 at the age of 8 routine examination disclosed irregularity of the pulse. Apart from the apparent epileptic fits he was free of symptoms. There was no history of syncope or sudden death in other members of the family. On examination the only abnormality was a slow and irregular pulse between 40 and 50 beats/minute. The electrocardiogram showed slow atrioventricular junctional rhythm with long periods of bigeminy (Fig. 1). Although long traces were recorded, at no time could normal sinus rhythm be recorded. In this boy, the possibility of a link between the arrhythmia and the syncopal attacks was not entertained. At the age of 10 he died suddenly while playing.

CASE 2

A 7-year-old white girl was first examined at the University Hospital of Kinshasa, Zaire, in 1968, because of attacks of dizziness and a slow heart rate. The family history was unremarkable. The electrocardiogram showed slow sinus rhythm, often below 40/min, atrial premature beats, and atrioventricular junctional escape beats. The bradycardia and fainting attacks were attributed to an excess of vagal tone. Isoprenaline, six times daily, was given and seemed to decrease the dizziness. In 1968 and 1969, however, two short episodes of loss of consciousness unrelated to effort were witnessed by her parents. When she was first seen by us in July 1969, the heart rate was 40 to 50/minute. A grade 2/6 ejection murmur and a short diastolic rumble at the apex were heard. As there was no other clinical evidence of heart disease, these murmurs were attributed to the slow heart rate and increased stroke volume. The electrocardiogram showed slow sinus rhythm, a PQ interval of 0·18–0·20 second and long atrial pauses of 1·8 to 2 seconds. On exercise the heart rate increased to 120/minute but, within 15 seconds, it slowed down and became irregular, a result of second and third degree sinuatrial block. From 1969 to 1974 she took no drugs. In 1974 she was admitted for further in-

Table 3 *Arrythmias in five children with congenital sick sinus syndrome*

Type of arrhythmia	*No. of patients*
Sinus bradycardia 40/min or below	5
Sinuatrial block (2nd or 3rd degree)	5
Predominant atrioventricular junctional rhythm	1
Atrial flutter or fibrillation	3
Ventricular tachycardia and fibrillation	1
Atrioventricular block (first or second degree)	2

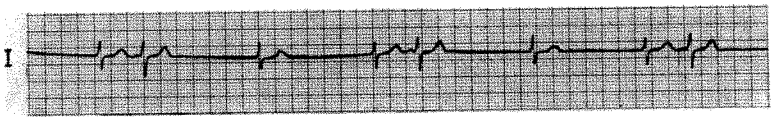

Fig. 1 *Electrocardiogram lead I from 8-year-old boy (case 1) showing slow junctional rhythm. The intermittent P waves and occurrence of bigeminy may be explained by slow retrograde conduction to the atria and reciprocal beats. Though long traces were obtained, at no time could normal sinus rhythm be recorded. The small irregularity of the T wave in complex 3 is artefactual.*

vestigation. Continuous monitoring showed extremely long pauses, up to four seconds, particularly at night (Fig. 2). In view of the extreme bradycardia, the insertion of a permanent pacemaker was recommended but this was refused by the parents as being unnecessary in an apparently healthy girl. In view of the risk of thromboembolic complications anticoagulants were started in 1974 and continued until the present. Cardiac rhythm remained unstable. In 1975 atrial flutter with 3:1 and varying atrioventricular conduction was recorded and a few weeks later slow sinus bradycardia with pauses up to three seconds. In 1976 and when last seen in 1978, once again she had atrial flutter, but now with varying atrioventricular conduction (Fig. 3). In the last 9 years under our care, she has had no further attacks of syncope. Her only symptom is an occasional episode of dizziness.

CASE 3

In December 1976 a 4-year-old boy was referred by the family doctor who had noted a slow and irregular heart rate during a fever. He had never fainted or had a fit. On examination the only abnormality was a bradycardia between 30 and 40/minute. The electrocardiogram showed sinus bradycardia and high-grade sinuatrial block (Fig. 4). In February 1977 regular sinus rhythm at 72/minute was noted. Four months later long periods of bradycardia were again recorded. Exercise increased the heart rate to 80 to 84/minute but this was followed within seconds by bradycardia, with long pauses caused by 3:1 sinuatrial block.

In September 1977 he collapsed while playing at school. According to his teacher he fell suddenly, and was found to be unconscious, and not breathing. He was given mouth-to-mouth respiration and within 10 minutes rushed to the emergency department of the hospital. On arrival he was still unconscious. The electrocardiogram showed periods of ventricular tachycardia (Fig. 5). He was intubated and cardioversion was carried out. Stable sinus rhythm, however, could not be restored. A few hours later a temporary transvenous pacemaker

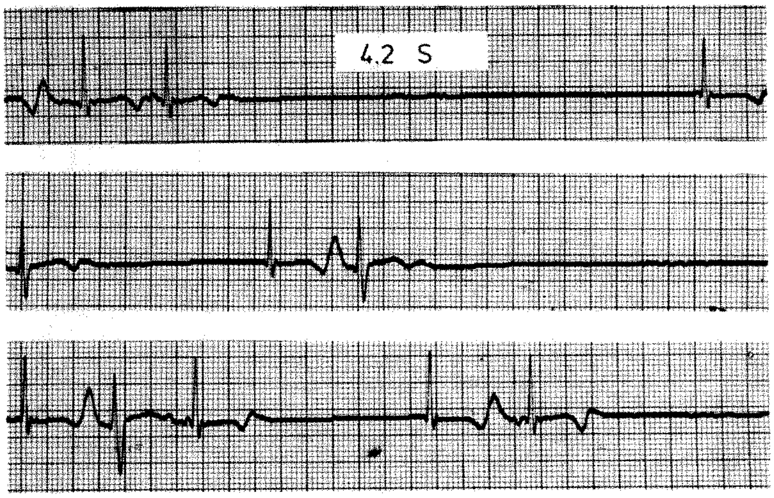

Fig. 2 *Continuous strip of a monitoring lead from a 12-year-old girl (case 2). Nocturnal heart rate dropped below 30 beats/min. The longest asystolic period (upper panel) was 4·2 seconds.*

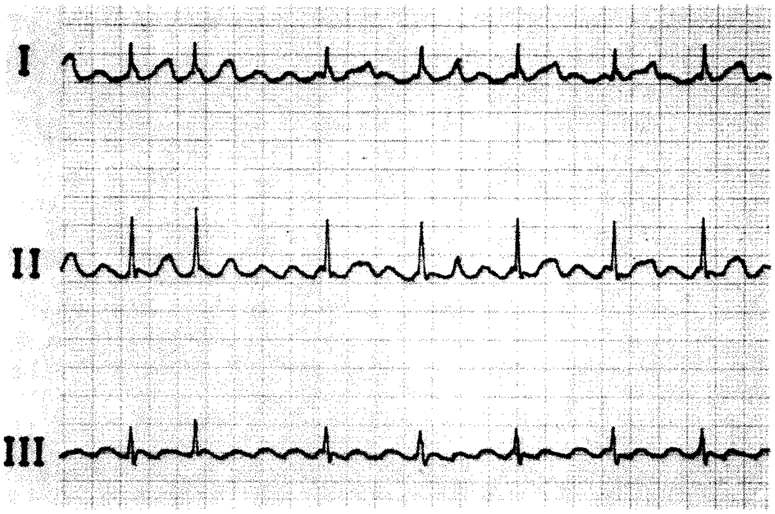

Fig. 3 *Leads I, II, and III in the same patient (case 2) two years later, showing atrial flutter with varying atrioventricular conduction.*

had to be introduced because of repeated episodes of ventricular tachycardia alternating with periods of atrial and ventricular standstill. The next day a permanent lithium demand pacemaker was inserted and extubation was possible. For three days he remained semiconscious and his gait was uncertain for several weeks. He eventually recovered completely. Subsequent electrocardiograms showed that the pacemaker was intermittently inactive, because of atrial flutter or fibrillation with a rapid ventricular response. This was treated with digoxin and quinidine.

CASE 4

A healthy newborn girl had had a slow fetal heart rate of 60/minute during the last days of pregnancy and during labour. At birth the rate remained at 60/minute but it increased to 90/minute over the next few days. When she was first examined at our department at 2 months of age, she was in regular sinus rhythm at 80/minute. Her rate increased to only 100/minute when she cried. At 14 months of age slow sinus rhythm at 46/minute was recorded. The PQ interval was 0·16 second. A few blocked P waves were noted. At the age of 3 fine atrial fibrillation with a ventricular response of 42/minute was observed, and this increased to only 52/minute when she ran 150 metres. On auscultation a grade 3/6 ejection murmur at the pulmonary area and a diastolic rumble at the apex were heard. These murmurs and cardiomegaly on the chest *x*-ray were attributed to the extreme bradycardia. Cardiac catheterisation showed no abnormality except a slightly increased systolic pressure in the pul-

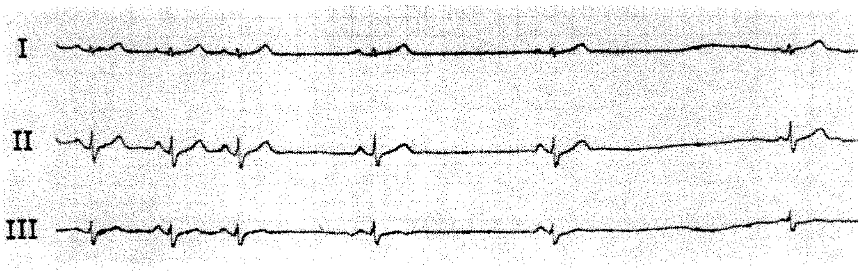

Fig. 4 *Leads I, II, and III from a 4-year-old boy (case 3). Progressive shortening of the sinus cycle (complexes 1 to 3) is followed by overt sinuatrial block. The third PP interval is exactly twice the second PP interval. The fourth PP interval equals three times the second PP interval minus 220 ms. This suggests coexisting first degree and 3:1 sinuatrial block. The morphology of the sixth P wave is different. It is probably an atrial escape beat.*

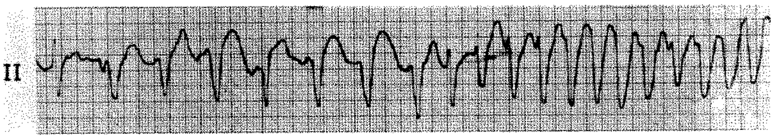

Fig. 5 *Lead II recorded in a 4-year-old boy (same case as in Fig. 4) during an episode of coma, after sudden collapse. Accelerated idioventricular rhythm leads to ventricular tachycardia.*

monary artery (36/12, mean 18 mmHg). Angiocardiography showed enlargement of the cardiac chambers but an otherwise normal heart. Continous 24-hour electrocardiographic monitoring showed fine atrial fibrillation with an irregular ventricular response varying between 30 and 96/minute by day, with occasional longer pauses up to four seconds. During the night the ventricular rate varied between 15 and 45/minute with exceptional peaks at 70/minute. One pause of 4·8, one of 4·6, and numerous pauses of more than 3 seconds were recorded. In spite of the extreme bradycardia the child was active and completely free of symptoms. This made management difficult as the parents were reluctant to accept that the child's condition was serious and potentially lethal, but in view of our experience with the previous patients insertion of a permanent pacemaker was advised. This has been carried out recently.

CASE 5

A 12-year-old boy gave a history of 10 to 12 brief syncopal attacks which had started at the age of 6 years. There had been no prodromal symptoms nor was there any relation to effort. He was a keen footballer and took part in various sports without symptoms. Physical examination was normal. The electrocardiogram showed regular sinus rhythm at 76 beats/minute and a prolonged PR interval (0·30 s). The QT interval was normal. Continuous 24-hour monitoring disclosed frequent episodes of second degree sinuatrial block, sinus arrest, and pauses lasting up to two seconds. For long periods nocturnal rates of 32 to 34 beats/minute were recorded. Exercise testing produced a normal rise in heart rate. Because of the possibility that physical training might have been contributing to this bradycardia, he was advised to give up football and to restrict strenuous effort. He was given isoprenaline 15 mg 12-hourly and has had no further syncopal attacks in the last two years

ELECTROPHYSIOLOGICAL STUDIES

Electrophysiological data were available in three patients. In case 2 the atrioventricular conduction and the sinus recovery time were normal. In case 3 only data obtained by chest wall stimulation were available. Inhibition of the permanent pacemaker produced atrial and ventricular standstill for 3·7 seconds. This observation shows the unrealiability of subsidiary escape mechanisms when the sinus node is failing. In case 4 intracardiac electrocardiography disclosed fine atrial fibrillation. After three minutes of right ventricular stimulation, ventricular standstill of 5·4 seconds occurred when pacing was stopped (Fig. 6). Similarly, when the permanent pacemaker was inhibited by chest wall stimulation, a pause of 3·5 seconds was recorded.

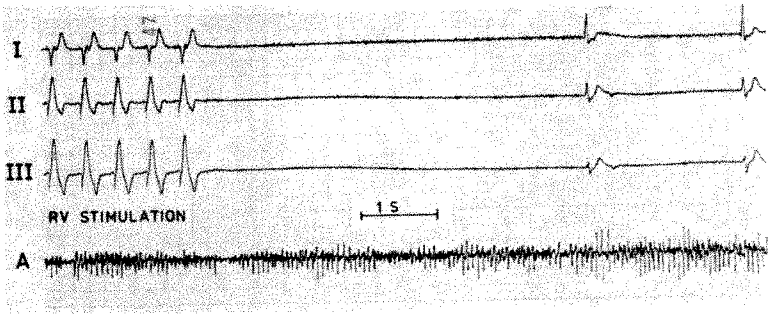

Fig. 6 *Leads I, II, III, and an intracardiac right atrial lead (A) in a 3-year-old girl (case 4) known since birth to have sick sinus syndrome and atrioventricular node dysfunction. The basic rhythm is fine atrial fibrillation. When intracardiac right ventricular stimulation (the first five beats) is stopped, it takes 5·4 seconds before a junctional escape beat appears.*

Discussion

The sick sinus syndrome in childhood is a well-known complication of cardiac surgery.[5 6] Its association with cardiac malformations[8–10] and with myocarditis[7 10] is equally well documented. In the present series, however, no underlying or associated heart disease could be detected. The term isolated sick sinus syndrome seems therefore appropriate. Approximately 20 similar cases have been published, a few well-documented case reports[13–17] and one extensive study.[11] In two other papers, dealing mainly with postoperative sinus node dysfunction, the occurrence of this syndrome in a few otherwise healthy children is mentioned.[7 10]

For inclusion in our small series deliberately strict criteria were applied, as little is known about the physiological variations of cardiac rhythm in normal infants and children. According to a recent study[18] the slowest heart rate in 134 randomly selected neonates was 93 ±12 beats per minute. In only one was bradycardia below 50 beats per minute and a systolic pause of 1·8 seconds recorded. In sleeping young adults rates may be as low as 33 beats per minute, but in only two out of 50 individuals were pauses of two seconds recorded.[19] It is therefore unlikely that any of our patients had physiological bradycardia.

The age at onset of symptoms in our patients (Table 1) is younger than in most of those previously reported. In one (case 4) bradycardia was noted before birth by the obstetrician, who suspected congenital atrioventricular block. The question therefore arises whether our patients and other young children previously reported[13 15 16] differ aetiologically from the adolescent group. All the patients reported by Scott *et al.*,[11] for instance, were athletic boys between 10 and 15 years. In our series, however, the hypothesis that excessive training might have produced bradycardia can be excluded, as most patients were below the age of 10 and, with the exception of one boy (case 5), did not take part in sports.

Four out of the five children presented with neurological symptoms—dizziness, fainting spells, or syncope (Table 1). One boy (case 1), who later died suddenly while playing, was treated for epilepsy before the underlying arrhythmia was diagnosed. Another (case 3), aged 5, had no symptoms until he suddenly collapsed with ventricular tachycardia, again while playing. Syncopal attacks on exertion were also noted by Scott *et al.*[11] and sudden death reported in two further cases.[15 20] Cerebrovascular accidents, common in adults with the bradycardia-tachycardia syndrome,[2] were not encountered in our patients but Onat *et al.*[13] described right-sided hemiparesis and facial weakness, presumably secondary to cerebral embolism, in a 3-year-old girl.

Three of the four children exercised were unable to increase their heart rate more than 30 per cent. An inappropriate response to exercise is generally considered to be a simple and reliable clue to the diagnosis.[9 11 15] Similarly, the response to the intravenous administration of atropine, which was not studied in our patients, is reported to be abnormal.[3 9 11] Continuous electrocardiographic monitoring, however, provides, in our experience, the best tool for evaluating patients suspected of having sinus node dysfunction. The information gained by this method is important from two points of view. In the first place, bradycardias and long pauses (Table 2), often unsuspected on the routine electrocardiograms, may be documented—in three of the children nocturnal rates dropped below 30 beats per minute and asystoles as long as 4·2, 3·5, and 4·8 seconds were recorded. Secondly, the full spectrum of arrhythmias is detected (Table 3)—atrial flutter or fibrillation was observed in three patients.

Supraventricular arrhythmias are so common in adults with the sick sinus syndrome[2–4] that it led to the use of the alternative term the bradycardia-tachycardia syndrome. They are also prominent in children with the postoperative sick sinus syndrome.[5 6]

By contrast, ventricular tachycardia or fibrillation have not been documented in large series of adults,[2 4] but seem to occur in children. In one patient (case 3, Fig. 5), the former caused a near-fatal syncope. Chaotic ventricular rhythm has also been reported in six previous cases.[7 14 15] Obviously, the association is too common to be fortuitous. It has been suggested that bradycardia favours desynchronisation of cardiac activation and thus the occurrence of ventricular tachycardia.[21 22] The finding that two patients had delayed atrioventricular conduction and therefore, presumably, binodal disease is of particular interest. This has also been found in three other children with this syndrome.[7 13 16]

Electrophysiological studies were of limited value. In one patient with severe bradycardia in whom a complete study was performed, atrioventricular conduction and sinus node recovery times were normal.

A previous study found a considerably prolonged sinus node recovery time in one child, but a normal one in another.[23] The occurrence of "false negative" electrophysiological testing and its interpretation have recently been reviewed in adults.[24] From the practical viewpoint, we accepted the diagnosis of the sick sinus syndrome on the basis of abnormal 24-hour electrocardiographic monitoring and exercise testing, even in the presence of a normal sinus node recovery time. In children with a permanent pacemaker, the spontaneous activity of the sinus node or subsidiary pacemakers can be assessed when the artificial pacemaker is temporarily inhibited by chest wall stimuli.

The histopathology of isolated sick sinus syndrome in children and adolescents has not been defined. The only pathological study, by James *et al.*,[25] found intimal proliferation and medial hypertrophy in the sinus node artery of two young athletes who died suddenly during exertion. The pre-existing rhythm, unfortunately, was not well documented. It appears reasonable, for a number of reasons, to postulate a congenital defect of the sinus node as the basic lesion, namely: (1) the syndrome may present in early childhood and, as documented for the first time in our study, even at birth, (2) it is occasionally associated with other cardiac malformations,[7–9] (3) more than one case may occur in a single family.[14 26 27] Moreover, a few families have been described in which both sinuatrial and atrioventricular node dysfunction were inherited.[26 28]

Because of the small number of children with isolated sick sinus syndrome so far described, and the wide spectrum of symptoms, a therapeutic policy is difficult to establish. Based on our experience in which one child died suddenly and another suffered a life-threatening ventricular arrhythmia we consider that permanent cardiac pacing is the only reliable treatment if symptoms are present or if they are not but the heart rate is very slow. Williams *et al.*[20] concur. In patients with tachycardia antiarrhythmic drugs and, possibly, anticoagulants should be used.

References

1 Bouvrain Y, Slama R, Temkine J. Le bloc sinoauriculaire et les "maladies du sinus": réflexions à propos de 63 observations. *Arch Mal Coeur* 1967; **60**: 753–73.

2 Rubenstein JJ, Schulman CL, Yurchak PM, Desanctis RW. Clinical spectrum of the sick sinus syndrome. *Circulation* 1972; **46**: 5–13.

3 Ferrer MI. The sick sinus syndrome. *Circulation* 1973; **47**: 635–41.

4 Rokseth R, Hatle L. Prospective study on the occurrence and management of chronic sinoatrial disease, with follow-up. *Br Heart J* 1974; **36**: 582–7.

5 Gillette PC, El-Said GM, Sivarajan N, Mullins CE, Williams RL, McNamara DG. Electrophysiological abnormalities after Mustard's operation for transposition of the great arteries. *Br Heart J* 1974; **36**: 186–91.

6 Greenwood RD, Rosenthal A, Sloss LJ, Lacorte M, Nadas AS. Sick sinus syndrome after surgery for congenital heart disease. *Circulation* 1975; **52**: 208–13.

7 Radford D, Izukawa T. Sick sinus syndrome. Symptomatic cases in children. *Arch Dis Child* 1975; **50**: 879–85.

8 Zetterqvist P. The syndrome of familial atrial septal defect, heart arrhythmia and hand malformation (Holt-Oram) in mother and son. *Acta Paediat (Stockholm)* 1963; **52**: 115–22.

9 Nugent E, Varghese P, Pierone D, Rowe R. Sluggish sinus node syndrome as part of congenital heart disease (abstract). *Am J Cardiol* 1974; **33**: 160.

10 Yabek SM, Jarmakani JM. Sinus node dysfunction in children, adolescents, and young adults. *Pediatrics* 1978; **61**: 593–8.

11 Scott O, Macartney FJ, Deverall PB. Sick sinus syndrome in children. *Arch Dis Child* 1976; **51**: 100–5.

12 Scherlag B, Lau S, Helfant R, Berkowitz W, Stein E, Damato A. Catheter technique for recording His bundle activity in man. *Circulation* 1969; **39**: 13–8.

13 Onat A, Domanic N, Onat T. Sick sinus syndrome in an infant. *Eur J Cardiol* 1974; **2**: 79–83.

14 Nordenberg A, Varghese PJ, Nugent EW. Spectrum of sinus node dysfunction in two siblings. *Am Heart J* 1976; **91**: 507–12.

15 Von Bernuth G, Lang D, Hofstetter R. Tachyarrhythmische Synkopen unter Belastung bei Sinusbradykardie und normalem QT-Intervall in Ruhe. *Z Kardiol* 1977; **66**: 55–60.

16 Stopfkuchen H, Jüngst B. Congenital sinus bradycardia combined with congenital total atrioventricular block. *Eur J Pediatr* 1977; **125**: 219–224.

17 Young D, Eisenberg R. Symptomatic sinus arrest in a young girl. *Arch Dis Child* 1977; **52**: 331–4.

18 Southall DP, Richards JM, Johnston PGB, Shinebourne EA. Study of cardiac rhythm in healthy newborn infant (abstract). *Br Heart J* 1979; **41**: 382.

19 Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. *Am J Cardiol* 1977; **39**: 390–5.

20 Williams W, Izukawa T, Olley P, Trusler G, Rowe R. Permanent cardiac pacing in infants and children. *Pace* 1978; **1**: 439–47.

21 Han J, Moe GK. Nonuniform recovery of excitability in ventricular muscle. *Circ Res* 1964; **14**: 44–60.

22 Krikler DM, Curry PVL. *Torsade de pointes*, an atypical ventricular tachycardia. *Br Heart J* 1976; **38**: 117–20.

23 Radford D, Izukawa T, Rowe R. Evaluation of children with ventricular arrhythmias. *Arch Dis Child* 1977; **52**: 345–53.

24 Reiffel JA, Bigger JT Jr, Cramer M, Reid DS. Ability of Holter electrocardiographic recording and atrial stimulation to detect sinus nodal dysfunction in symptomatic and asymptomatic patients with sinus bradycardia. *Am J Cardiol* 1977; **40**: 189–94.

25 James TN, Froggatt P, Marshall TK. Sudden death in young athletes. *Ann Intern Med* 1967; **67**: 1013–21.

26 Sarachek NS, Leonard JJ. Familial heart block and sinus bradycardia, classification and natural history. *Am J Cardiol* 1972; **29**: 451–8.
27 Lehmann H, Klein UE. Familial sinus node dysfunction with autosomal dominant inheritance. *Br Heart J* 1978; **40**: 1314–6.
28 Schneider MD, Roller DH, Morganroth J, Josephson M. The syndromes of familial atrioventricular block with sinus bradycardia: prognostic indices, electrophysiologic and histopathologic correlates. *Eur J Cardiol* 1978; **7**: 337–51.

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Differential atrial filling after Mustard and Senning repairs

Detection by transcutaneous Doppler ultrasound

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SUMMARY The dominance of Mustard's operation for transposition of the great arteries has been challenged by the recent revival of Senning's repair because it promises better long-term results in terms of venous obstruction and atrial haemodynamics. These hypotheses were tested by recording jugular venous flow waveforms transcutaneously in 24 postoperative patients with simple complete transposition using a bidirectional Doppler blood velocimeter. Eight patients had undergone Mustard's operation and 16 the Senning alternative; all had previously had a postoperative cardiac catheterisation.

Both groups of patients had similar left ventricular, pulmonary arterial, and systemic venous atrial pressures. No child showed any evidence at catheterisation of either mitral regurgitation or of superior vena caval pathway obstruction. These two findings were endorsed by the transcutaneous Doppler recordings.

Jugular venous flow in normal children exhibits two maxima, one of atrial filling during ventricular systole, the other of ventricular filling occurs once the tricuspid valve has opened. Both operative procedures diminished the size of the former phase, but the Mustard did so more. After Mustard's operation forward flow during the atrial filling phase was absent in approximately half the cardiac cycles recorded, and severely diminished in the rest. By contrast, there was approximately a 90 per cent appearance of atrial filling waves after Senning's operation which also provided significantly better atrial function than Mustard's procedure in terms of peak velocity of blood entering the atrium and total atrial filling. It is therefore concluded that both procedures compromise atrial volume and compliance but Senning's repair to a much lesser extent.

The Senning operation[1] has recently been revived as an alternative form of treatment to the Mustard procedure[2] for the physiological correction of complete transposition of the great arteries by the decussation of venous inflow.[3] This recent challenge to Mustard's procedure was prompted because of the impressive haemodynamics of some children with 16-year-old Senning repairs, showing no signs of venous stenosis. Such obstruction to inferior and superior vena cavae and to the pulmonary veins is an important cause of late morbidity and mortality after Mustard's procedure[4] despite low initial mortality.[5–7] Patches of pericardium used in Mustard's procedure may become infected, contract, or develop structural defects.[8] Dacron patches were therefore introduced, but though immediate postoperative survival improved, a high proportion of these children subsequently developed obstruction to venous return, requiring surgical revision.[7 9] If the interatrial baffle is too large it can lead to pulmonary venous obstruction; if it is too small the superior or inferior vena caval pathway or both will become stenosed. Despite refinements,[7 10] the interatrial baffle still creates an inherent confinement of atrial movement, a reduced atrial filling capacity, and a potential for venous obstruction and infective endocarditis.

The geometry of the Senning operation is such

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that stenosis of the vena cavae is nearly impossible and pulmonary venous obstruction may be avoided with operative care. Perhaps more importantly, the amount of foreign material used is small, even after a previous atrial septectomy[11]; reconstruction is mainly of living atrial muscle. This has two potential advantages; firstly, the atrium may be expected to grow as the patient grows, and secondly, the atria may function better as each will be contracting against a yielding, compliant partner rather than against a stiff, immobile prosthesis, as in the Mustard procedure. It has already been shown that the large interatrial baffle used in Mustard's procedure dramatically reduces the rate of filling of the systemic venous atrium, probably by serious loss of atrial compliance and volume[12]; this is also manifested in the systemic venous atrial pressure pulse by a steep y descent.[13] Even disregarding the effect of atrial growth, however, the design of the Senning operation (that is, pulmonary venous blood being redirected outside the atrial wall) suggests that not only atrial compliance but also atrial volume should be less compromised than in Mustard's procedure.

We felt that this hypothesis could be tested non-invasively using transcutaneous Doppler ultrasound to measure jugular venous velocity flow patterns which reflect derangements in right heart haemodynamics irrespective of the underlying aetiology.[14] This technique has been used successfully to diagnose asymptomatic superior vena caval pathway obstruction after Mustard's procedure,[12] and it seemed therefore appropriate to apply it to Senning's repair, firstly to screen for obstruction, however unlikely,[3] and secondly to compare compromise of atrial function after the Mustard and Senning procedures.

Methods

Jugular venous flow velocity recordings were made in 24 patients who had previously been corrected for simple complete transposition of the great arteries at the University Hospital, Leiden. Sixteen (age range 1·7 to 5·6 years, mean 3·6) had Senning and eight (age range 6·0 to 12·6 years, mean 9·8) had Mustard repairs. Patients were tested sequentially at special outpatient clinics. A transcutaneous bi-directional Doppler ultrasound blood velocimeter* was used, which incorporated a three-lead electrocardiogram and a flow channel, plotting them both onto an integral paper chart recorder. The machine also emits an audible tone whose frequency is proportional to the velocity signal. The transmitter frequency was 7·52 MKz.

Patients were quiet and supine with no pillow and the head turned slightly away from the examiner to expose the jugular vein. The limb leads of the electrocardiograph were attached to the patient and the instrument checked for an appropriate electrocardiographic deflection (showing the p waves in particular) on the recording paper. The external probe was applied to the skin using Aquasonic 100 ultrasound transmission gel.† The probe was placed over the internal jugular vein and directed toward the inferior border of the contralateral scapula. Its position was then adjusted until the signal reached a maximum. When this signal was consistent, reproducible, and pure, that is free from components of flow from adjacent arteries, the electrocardiogram and jugular flow signals were then recorded simultaneously on the chart recorder at a paper speed of 50 mm/s using a foot switch control. Recordings were obtained whenever possible from both left and right jugular veins, after which a recording of the carotid velocity trace was also made to verify by comparison that there was no arterial component in any of the venous flow recordings. Zero flow was recorded routinely and regularly as a reference level and both venous and arterial forward flows were displayed as positive deflections by the appropriate use of the reversal switch, standard to this instrument.

Areas under flow velocity curves were calculated as follows. First, the original traces were photocopied. Second, areas were then measured both by planimetry (Allbrit Planimeter‡) and by weighing (Stanton CL4D§) each carefully dissected photocopied flow velocity waveform. The latter method was found to be considerably more accurate and reproducible than planimetry. Values for each patient are the means of seven to 20 cardiac cycles, depending upon availability. Only those cardiac cycles showing both atrial and ventricular filling waves were selected for this portion of the study.

All patients had previously undergone a standard postoperative cardiac catheterisation to assess their haemodynamic status.

Results

POSTOPERATIVE CARDIAC CATHETERISATIONS

These data are summarised in Table 1. Patients in the Mustard and Senning groups could not be distinguished from one another by pressures in the left ventricle, pulmonary artery, or systemic venous atrium, or by the left ventricle to pulmonary artery pressure gradient. Additionally, none of these four variables was found to correlate with any of the height or area ratios derived from the velocity traces.

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*Sonicaid Ltd. Model BV381.

†Parker Laboratories, New Jersey, USA.
‡Stanley and Co, London.
§Stanton Ltd, London.

There was no evidence of mitral regurgitation in any of the children.

Table 1 *Postoperative catheterisation results in patients corrected for transposition*

	LV (mmHg)	*PA (mmHg)*	*LV–PA gradient (mmHg)*	*Systemic venous atrium (mmHg)*
Mustard	32·9 ±3·1	23·0 ±2·2	9·9 ±2·7	5·8 ±1·1
Senning	34·6 ±2·9	21·9 ±0·9	12·8 ±3·0	7·5 ±0·8
	NS	NS	NS	NS

Values are means and standard errors. NS, not significant.

DIAGNOSIS OF SUPERIOR VENA CAVAL PATHWAY OBSTRUCTION

Criteria for the non-invasive diagnosis of superior vena caval pathway obstruction using transcutaneous bidirectional Doppler ultrasound recordings from the jugular vein have already been published[12] and Doppler recordings taken from children of both the groups in this study were similarly examined for signs of obstruction. No such signs were apparent in any of the children and this finding was supported by data obtained from each of the children at postoperative cardiac catheterisation. No gradient higher than 1 mmHg between the superior vena cava and the systemic venous atrium was found in any of the children from the Mustard group, and none higher than 4 mmHg found in the Senning group (the two in this group with a 4 mmHg gradient showed no signs of azygos filling during a superior vena caval angiogram).

COMPARISON OF ATRIAL FUNCTION AFTER MUSTARD AND SENNING PROCEDURES

A typical example of the jugular venous flow velocity trace seen before the current study in a number of normal children is shown in Fig. 1. Similar patterns have been observed by other workers.[4–16] These patterns are characterised by two waves of forward flow. The first, of atrial filling during ventricular systole, is the result of a combination of atrial relaxation and tricuspid descent. The second, in ventricular diastole, reflects filling of the ventricle once the tricuspid valve has opened. The two maxima of forward flow are followed by a wave of reduced or reverse flow coinciding with and probably caused by the atrial systole of the next cardiac cycle.

The pattern seen in most post-Mustard cases is shown in Fig. 2a. It is characterised by a partial or total loss of the forward flow wave in ventricular systole and by no reversal of flow during atrial systole. A typical jugular flow pattern seen in post-Senning cases is shown in Fig. 2b. Forward flow velocity in ventricular systole was also reduced compared with normals but much less so than in the post-Mustard cases, with definite ventricular systolic maxima seen in most or all cardiac cycles. When the relative incidence of atrial filling waves over the entire record of cardiac cycles for each patient was measured and means calculated for each group, the results showed that atrial filling waves were significantly more frequent after Senning's procedure than after the Mustard alternative (Table 2).

The jugular venous velocity waveforms were then analysed in two further ways, as shown in Fig. 3. Mean relative height and area ratios for post-Mustard and post-Senning patients are presented

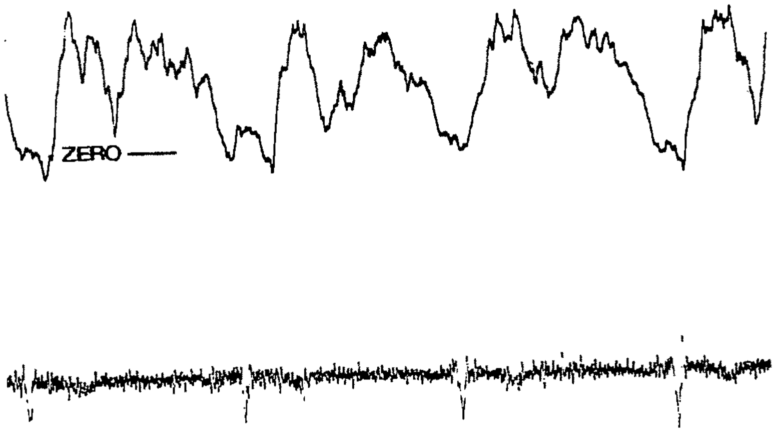

Fig. 1 *Jugular venous flow in a normal child. Flow towards the heart is depicted as above the zero line. There are two maxima of forward flow, the first during ventricular systole is of atrial filling. The second, in ventricular diastole, occurs once the tricuspid valve has opened.*

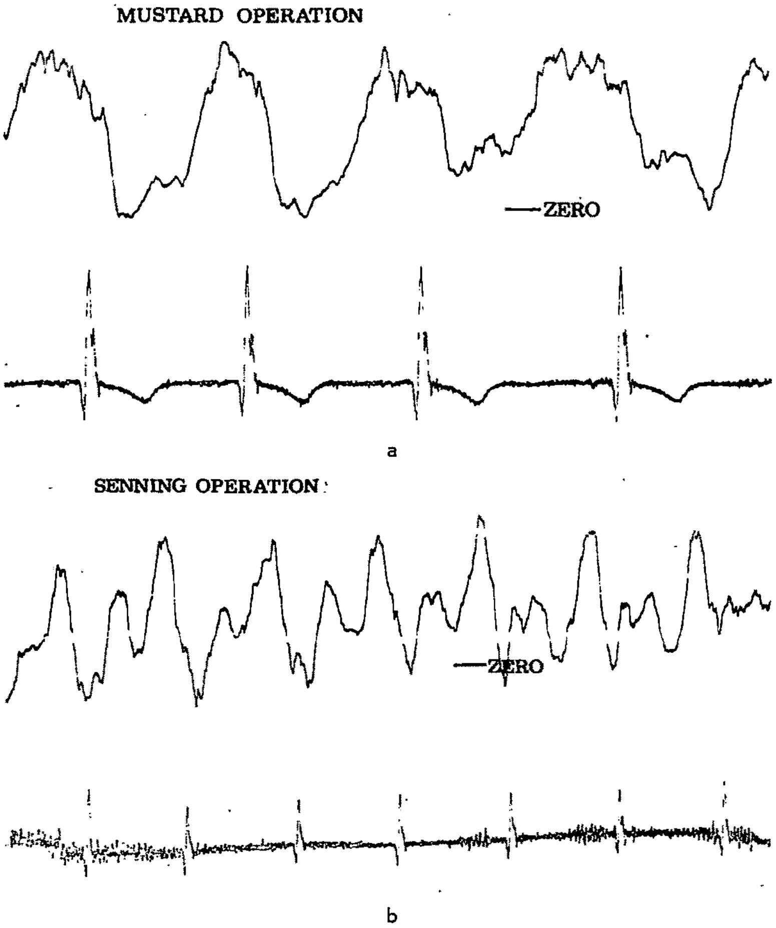

Fig. 2 *Typical jugular venous flow velocity recordings in patients after surgical correction of transposition of the great arteries. Flow towards the heart is depicted as above the zero lines. Fig 2a shows that after Mustard's procedure forward flow during ventricular systole (atrial filling phase) is almost or entirely lost. Fig 2b shows that though atrial filling is not as good in Senning's repair as in normal children, it is substantially better than in Mustard's procedure in terms of its incidence, rate, and volume.*

in Table 3. These results show that the relative height ratio is significantly higher ($p < 0{\cdot}05$) for Senning's operation (0·613) than for Mustard's procedure (0·455). The difference between the area ratios was even more pronounced, with the value for Senning's operation (0·436) significantly higher than the value for Mustard's procedure (0·226).

Discussion

The results have indicated that atrial filling characteristics after the Mustard and Senning procedures are qualitatively and quantitatively different. The data give no information on the relative ventricular filling characteristics. As the two groups of patients were statistically inseparable, however, in terms of their left ventricular and pulmonary arterial pressures (and their mean difference) it may be assumed that their ventricular function was similar.

The dominant factor producing forward jugular flow in ventricular systole is uncertain. There is some evidence[14] that in patients without transposition, tricuspid descent with a closed tricuspid valve is more important than atrial relaxation in promoting systolic superior vena caval flow. In post-Mustard patients the mitral valve may well be restrained from normal descent by the baffle. This, in combination with reduced atrial volume and compliance, tends synergistically to diminish forward venous flow in ventricular systole.

The fact that there was no clinical or angiographic evidence of mitral regurgitation in any of the patients is supported by the ultrasonic results. Tricuspid regurgitation in patients without transposition creates retrograde jugular venous and superior vena caval flow during ventricular systole[14 17 18] and similar results would have been expected in patients in the current study if mitral regurgitation were present after Mustard's or Senning's procedure.

The inequality of the mean ages of the two groups examined in this study was because the Mustard operation was largely discontinued in Leiden some time ago in favour of Senning's procedure. While it is clear that ideally the groups would be identical in terms of current age and also their age at operation, it is perhaps relevant to point out that the jugular venous velocity flow pattern in normal children changes little with age. Therefore, for children in the current study, with no caval obstruction or impaired mitral valve function, change with time in jugular flow characteristics would not be anticipated. This is also supported by the experience of jugular venous flow velocity recordings made in children of all ages after the Mustard operation at Great Ormond Street Hospital.

Table 2 *Relative incidence of atrial filling waves per 100 cycles in jugular venous flow velocity recordings*

Mustard	56 ±11
Senning	89 ±2
	p<0·01

Values are means and standard errors.

Jugular venous flow velocity traces seen in post-Mustard cases without caval obstruction at Leiden were indeed similar to those seen at Great Ormond Street Hospital in a previous study[12] except that atrial filling may have been slightly better in the latter group. We did not wish to include this latter group in the current data, however, because it represented the addition of another variable (that is slightly different surgical techniques).

Table 3 *Dimensions of atrial filling waves compared with ventricular filling waves*

Mustard versus Senning—Atrial filling	*Height ratio*	*Area ratio*
Mustard	0·455	0·226
Senning	0·613	0·436
	—	—
t	2·322	4·870
p	<0·05	<0·001

Note: Height ratio is result of dividing peak height of atrial filling wave by peak height of ventricular filling wave and is thus a measure of relative blood velocities. The area ratio is similarly a measure of relative total blood flow during two filling phases.

It can be difficult to make ultrasonic transcutaneous jugular venous flow velocity recordings in children because they often only keep still and silent while a few consecutive waveforms are recorded. Consequently traces may consist of noisy, useless information interspersed with the data of interest. Recordings taken in this study were no different, but subsequent recognition of those noiseless traces that are derived from jugular venous flow only is never difficult even to the inexperienced eye.

The comparison of height and area ratios in the present study contains an inherent inaccuracy because atrial filling waves were significantly less frequent in the Mustard group (Table 2). As only those cardiac cycles with atrial filling waves could be analysed in terms of height and area ratios, disproportionate values must result. Atrial filling waves occurred only 56 per cent of the time in the Mustard group. The true value of the ratios is therefore

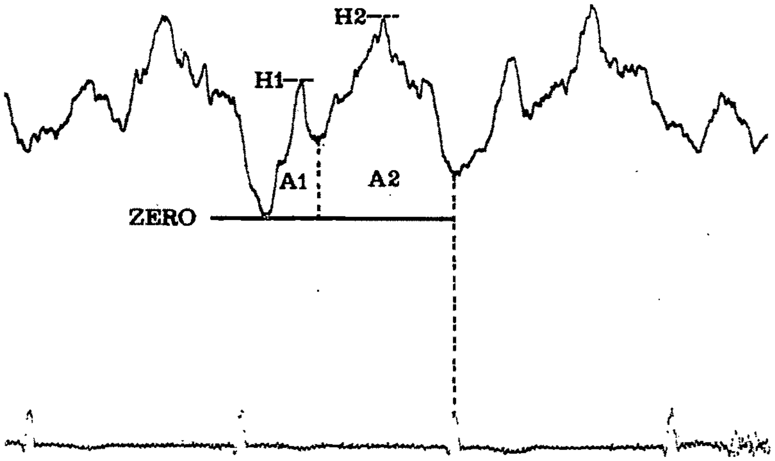

Fig. 3 *This is a jugular venous velocity recording from a patient after Senning's repair. Height ratios in all patients were determined by dividing the distance from zero to H1 by the distance from zero to H2. Mean values for each patient were derived by measuring many cardiac cycles, and these means were then pooled to give the group data. A similar process was used in determining the means of the area ratios A1/A2.*

overestimated by a factor of approximately two. The value of 89 per cent, however, for the Senning patients suggests that the overestimation of the ratio in this group is only of the order of 10 per cent. The effect of this transformation is that Table 3 is substantially biased in favour of the Mustard results. Despite this, the ratios are both significantly better for the Senning group. The haemodynamic significance of the height ratio is that it reflects the absolute velocity of blood along the jugular vein during the atrial and ventricular filling phases. The height of the atrial filling wave will be influenced by a number of factors, notably, the ability of the mitral floor to descend during ventricular systole, atrial compliance, and the rate of atrial relaxation. Though this ratio was significantly different in the two groups it is not possible to say which of the above factors is predominantly responsible for this difference. Though the Mustard baffle would probably affect the former two, in Senning's repair there is physically more live atrial muscle to relax.

The relevance of the area ratio is that it reflects the total volume of blood passing along the jugular vein during the atrial and ventricular filling phases. Therefore, this ratio gives an indication of atrial capacity, which is affected not only by the variables controlling the height ratio but also by physical size. Sequential studies on these patients would be required to ascertain whether these ratios do change with time; if the atria grow with the patient in Senning's repair then this might perhaps lead to consistent ratios throughout life. The static, non-growing nature of Mustard's repair might lead one to suspect that ratios are better in the immediate postoperative period than in the ensuing years as the patient grows. Jugular venous flow velocity recordings in many such children at Great Ormond Street Hospital suggests, however, that this is not so, and that the remaining atria may grow sufficiently to prevent further reduction of the ratios.

Ratios were highly consistent for the Senning group. In the group of eight Mustard patients, however, six had poor ratios but two were as high as any in the Senning group, showing that good atrial filling can occur in some patients despite the interatrial baffle. The fact that none of these ratios for either operation correlated with the haemodynamics supports the view that they are principally affected by physical restraints placed upon the atria as well as the limitations of atrial volume and compliance rather than by the pressures and gradients beyond the mitral valve.

Since the haemodynamics of the Mustard and Senning groups were statistically inseparable and there was also no correlation between ratios and haemodynamics, we may conclude from the results that the Senning operation compromises atrial volume and compliance less than Mustard's procedure. We cannot necessarily conclude that the Senning operation is the treatment of choice. A large alteration in atrial filling might have a relatively small effect on total cardiac performance, and systemic venous return is but one aspect of the comparison required. Pulmonary venous return, ventricular function, and arrhythmias are also important. Furthermore, with longer follow-up, the differences between the two groups might diminish. At the University Hospital, Leiden, there is currently a total commitment to the Senning operation if repair of transposition by redirection of venous inflow is sought. At The Hospital for Sick Children, Great Ormond Street, however, both the Mustard and Senning operations are still being evaluated; the present policy is for one surgeon to perform only Senning's repair and the other only Mustard's procedure. It is hoped that ultimately a consistent surgical approach to transposition of the great arteries will be reached in the light of the current study, data reflecting long-term morbidity and mortality, and the results of alternative procedures such as the arterial switch.

References

1 Senning Å. Surgical correction of transposition of the great vessels. *Surgery* 1959; **45:** 966–80.
2 Mustard WT. Successful two-stage correction of transposition of the great vessels. *Surgery* 1964; **55:** 469–72.
3 Quaegebeur JM, Rohmer J, Brom AG. Revival of the Senning operation in the treatment of transposition of the great arteries. *Thorax* 1977; **32:** 517–24.
4 Macartney FJ, Taylor JFN, Graham GR, de Leval MR, Stark J. The natural history of congenital heart disease as modified by cardiac surgery in the first year of life. In: Harper PS, Muir JR, eds. *Advanced medicine. No 15.* Tunbridge Wells: Pitman Medical, 1979: 1–13.
5 Aberdeen E. Correction of uncomplicated cases of transposition of the great arteries. *Br Heart J* 1971; **33,** suppl: 66–8.
6 Danielson GK, Mair DD, Ongley PA, Wallace RB, McGoon DC. Repair of transposition of the great arteries by transposition of venous return. Surgical considerations and results of operation. *J Thorac Cardiovasc Surg* 1971; **61:** 96–103.
7 Stark J, de Leval MR, Waterston DJ, Graham GR, Bonham-Carter RE. Corrective surgery of transposition of the great arteries in the first year of life. *J Thorac Cardiovasc Surg* 1974; **67:** 673–81.
8 Stark J, Tynan MJ, Ashcraft KW, Aberdeen E, Waterston DJ. Obstruction of pulmonary veins and superior vena cava after the Mustard operation for transposition of the great arteries. *Circulation* 1972; **45 & 46,** suppl 1: 116–20.

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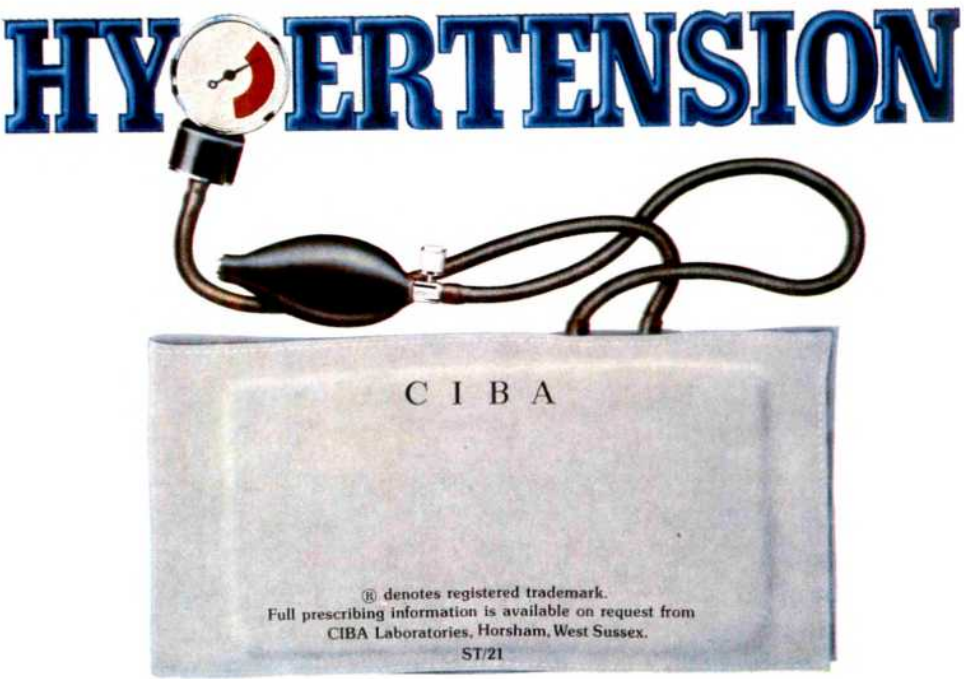

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Unsuspected coronary artery disease as cause of chronic atrioventricular block in middle age

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SUMMARY Attention has recently been drawn to the relatively poor prognosis of middle aged patients paced for chronic atrioventricular block when age-linked expectation of life is taken into account, and it has been suggested that this may be the result of underlying coronary artery disease, despite the absence of symptoms to suggest this. It was the purpose of this study to determine the incidence of unsuspected coronary artery disease in middle aged patients presenting with chronic atrioventricular block.

Studies were made on a consecutive series of 30 patients aged 45 to 65 (mean age 56 years) with chronic atrioventricular disease who had been referred for pacing. Patients presenting with acute myocardial infarction or angina or with sinuatrial disease without atrioventricular disease were excluded. Coronary arteriography disclosed the presence of severe coronary artery disease in 13 patients. Of the remaining 17 patients, four had congestive cardiomyopathy, two had hypertrophic cardiomyopathy, one had aortic stenosis, and in 10 patients the aetiology of the heart block was unknown.

Myocardial revascularisation was undertaken in six patients with paroxysmal atrioventricular block caused by coronary artery disease. Operation did not result in any sustained improvement in atrioventricular conduction.

Now that the technique of permanent pacing is well established in the management of chronic atrioventricular block, it seems likely that long term prognosis is dependent upon the aetiology of the heart block and in particular whether it is caused by idiopathic bundle-branch fibrosis, coronary artery disease, or cardiomyopathy. Attention has been drawn to the relatively poor prognosis of middle aged patients paced for chronic atrioventricular block when compared with older patients, if expectation of life, in relation to age, is taken into account, and it has been suggested that the poorer outlook in such patients is a result of the presence of underlying coronary artery disease.[1]

It was the purpose of this study to determine the incidence of occlusive coronary artery disease in middle aged patients presenting with evidence of chronic atrioventricular block and to assess the role of coronary vein bypass surgery in the treatment of such conduction disorders when paroxysmal.

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Patients and methods

Since 1976 we have investigated, by cardiac catheterisation and coronary arteriography, all patients aged 65 years or less who were referred for pacing because of chronic atrioventricular conducting tissue disease.

Thirty patients, eight women and 22 men, with an average age of 56 years, fulfilled these criteria. Patients with rhythm disturbances after acute myocardial infarction and patients with sinuatrial disease without atrioventricular disease were excluded.

Electrocardiographic monitoring at the bedside was undertaken in all cases and a portable 24 hour electrocardiogram was also obtained with an Avionics composite electrocardioscanner. In 12 patients, intracardiac electrocardiographic studies were performed in order to determine the mechanism of heart block.[2] Cardiac catheterisation was undertaken in all patients and the coronary artery anatomy was defined using the technique described by Sones and Shirey,[3] severe disease in the lumen of the major coronary arteries being defined as 70 to 100 per cent stenosis.

Results

The clinical data of the 30 patients are shown in Table 1. The majority of patients presented with dizziness or syncope. There were three patients in whom the primary complaint was dyspnoea. Two patients were free of symptoms. Five patients admitted to mild chest discomfort which was insufficiently severe to report to their referring physician. In one of them a history of myocardial infarction 11 years before was elicited.

Table 1 *Clinical data on patients with chronic atrioventricular block*

No. of patients	30
Age	56 (range 45 to 65 years)
Sex	
Male	22
Female	8
Presenting complaint	
Syncope	19
Dizziness	6
Dyspnoea	3
No symptoms	2

Of the 30 patients, atrioventricular block was paroxysmal in 17 and permanent in 13. The electrocardiographic findings are shown in Table 2. Three of the 17 patients with intermittent atrioventricular block had QRS complexes of normal duration, and conduction delay was considered to be proximal to the bundle of His. The remaining 14 patients with paroxysmal atrioventricular block had electrocardiographic evidence of bifascicular block; atrioventricular block was therefore considered to be the result of impaired conduction distal to the bundle of His, and this was confirmed in seven of the patients who underwent intracardiac electrocardiography.

Table 2 *Electrocardiographic findings in 30 patients with atrioventricular block*

Intermittent		17
QRS <0·12 s	3	
RBBB+LAH	6	
LBBB	7	
RBBB alternating LBBB	1	
Permanent		13
QRS <0·12 s	3	
QRS >0·12 s	10	

LAH, left anterior hemiblock; RBBB, right bundle-branch block; LBBB, left bundle-branch block.

Thirteen patients had permanent atrioventricular block. Three of these had a QRS complex of normal duration, and conduction delay was considered to be the result of block at atrioventricular or intra-Hisian level. The remaining 10 patients had a QRS duration of greater than 0·12 s and were considered to have infraHisian conduction delay.

Table 3 *Angiographic findings in 30 patients with atrioventricular block*

Normal	10
Severe coronary artery disease	13
Congestive cardiomyopathy	4
Hypertrophic cardiomyopathy	2
Aortic stenosis	1

The results of further investigations in the 30 patients with atrioventricular block are shown in Table 3. Thirteen patients had severe coronary artery disease. The remaining 17 patients had either insignificant or no coronary disease; two of these 17 had hypertrophic cardiomyopathy, four patients had congestive cardiomyopathy, one had severe aortic stenosis, and 10 patients had no evidence of additional heart disease. Those patients without evidence of coronary artery disease as a cause of atrioventricular block were managed by permanent endocardial pacing.

Table 4 *Distribution of coronary artery disease in 13 patients with atrioventricular block and related His bundle findings*

Distribution of coronary artery disease	*No. of patients*	*AV nodal block*	*InfraHisian block*
Right, LAD+diagonal, circumflex+marginal arteries	4	1	3
Left main stem, LAD+diagonal, circumflex arteries	1	–	1
Right, LAD+diagonal arteries	3	–	3
Right coronary+circumflex arteries	1	–	1
LAD+diagonal arteries	2	–	2
Right coronary artery only	2	2	–

Of the 13 patients with coronary artery disease and atrioventricular block, left ventricular angiography was considered normal in five patients and abnormal in eight. The distribution of the coronary artery disease in these patients is shown in Table 4, and these results show that three of the 13 patients with coronary artery disease and atrioventricular block had delay proximal to the bundle of His and severe stenosis or occlusion of a dominant right coronary artery; 10 had conduction delay distal to the bundle of His associated with left anterior descending coronary artery stenosis, proximal to or involving the origin of the first septal perforating artery in eight cases. There were nine patients with coronary artery disease and paroxysmal atrioventricular block and the other four patients had permanent atrioventricular block.

Myocardial revascularisation by coronary vein bypass grafting was undertaken in six patients with paroxysmal atrioventricular block caused by coronary artery disease. Five patients before operation had had recurring paroxysmal atrioventricular block, shown by intracardiac electrocardiography to be infraHisian in site. After operation in each case there was a temporary return to sinus rhythm during the first few postoperative days but this was followed by a recurrence of paroxysmal atrioventricular block. These patients had demand endocardial pacemakers inserted before hospital discharge.

The remaining patient had had infrequent episodes of atrioventricular block and the effect of operation was difficult to assess. This patient, however, has remained symptom free in the 12 months since operation without the need for permanent pacing.

Discussion

The aetiology of chronic atrioventricular block is frequently difficult to determine in the living patient.[4] Even a history of cardiac pain on effort may not indicate coronary disease since it may be secondary to slow heart rates or to cardiomyopathy. Coronary disease was undoubtedly implicated too often in the past,[5–9] and factors exaggerating its importance were the not uncommon precipitation of acute heart block by infarction and electrocardiographic evidence of changing T waves which may not be recognised as simply occurring secondary to pacing.[10] In this series the electrocardiogram was of no value in predicting the presence of underlying coronary disease. It was of interest that the majority of patients had a wide QRS complex and this observation compares closely with our clinicopathological findings in a series of 134 patients with chronic complete heart block of whom 111 had a QRS duration of greater than 0·12 s.

The incidence of coronary artery disease as a cause of chronic heart block in the elderly was studied at necropsy by Davies.[11] In a series of 100 patients (mean age 70 years) he found that only 15 per cent of the patients had coronary artery disease of sufficient severity to account for the heart block. Thus, isolated disease of the conduction tissue was the most common cause of chronic atrioventricular block and this explains the relatively normal expectation of life once paced.[12] Younger patients do not fare as well when age-linked expectation of life is taken into account[1] and the finding of severe coronary disease in 13 of the present series of 30 patients probably accounts for this observation. The incidence of coronary artery disease in a controlled normal population of similar age is unknown. Indirect evidence taken from patients undergoing isolated aortic valve replacement for a congenitally bicuspid valve or mitral valve replacement for rheumatic mitral valve disease suggests the presence of additional unrelated coronary artery disease in approximately 20 per cent of patients.[13 (and unpublished data)] Thus, the higher incidence of coronary artery disease in those patients with chronic atrioventricular block makes it the likely cause of the conduction disturbance rather than an associated finding.

An understanding of the pathological processes involved in the production of atrioventricular block by coronary artery disease can only be based on knowledge of the blood supply to the conduction system. The most elegant demonstration of this aspect is the work of James and Burch[14] using a vinylite injection technique. In 43 human hearts examined, the coronary artery which crossed the posterior crux of the heart (right 83%, left 7%, and both 10%) supplied the atrioventricular node, main bundle, and the origins of the bundle-branches. The bulk of the interventricular system was supplied by long penetrating branches derived from the anterior descending coronary artery. The anatomical findings of James and Burch have been confirmed in a post-mortem angiographic study of 192 human hearts.[15] On a theoretical basis in man, right coronary artery occlusion would cause nodal ischaemia and conduction delay proximal to the bundle of His; left anterior descending occlusion would cause bundle-branch ischaemia and delayed conduction distal to the bundle of His.

In our study, it was therefore of considerable interest to find a direct relation between the anatomical distribution of the coronary disease and the level of atrioventricular block, a correlation which appears to hold more closely for left anterior descending disease than for right coronary artery disease, though an isolated right coronary stenosis was an uncommon finding.

When heart block is paroxysmal in patients with obstructive coronary artery disease it is tempting to consider coronary vein bypass surgery in their management but so far the results have been disappointing. The early return to sinus rhythm observed in all patients during the perioperative period was presumably related to increased sympathomimetic drive. Coronary artery bypass grafting conceivably improved conduction in the one patient with conduction delay proximal to the bundle of His. The lack of success in the remaining cases probably reflects irreversibility of conducting tissue damage.

In conclusion, this study indicates that there is a high incidence of severe coronary artery disease in those patients less than 65 years of age with chronic atrioventricular block (13 of 30 cases). In addition, there was a close relation between the level of the heart block and the distribution of the coronary artery disease. Lastly, coronary bypass surgery proved to be ineffective in improving distal atrioventricular conduction in those patients with paroxysmal atrioventricular block which was considered to be a result of occlusive coronary artery disease.

References

1 Ginks W, Leatham A, Siddons H. Prognosis of patients paced for chronic atrioventricular block. *Br Heart J* 1979; **41**: 633–6.
2 Scherlag BJ, Lau SH, Helfont RH, Berkowitz WD, Stein E, Damato AN. Catheter technique for recording His bundle activity in man. *Circulation* 1969; **39**: 13–8.
3 Sones FM Jr, Shirey EK. Cine coronary arteriography. *Mod Concepts Cardiovasc Dis* 1962; **31**: 735–8.
4 Harris A, Davies M, Redwood D, Leatham A, Siddons H. Aetiology of chronic heart block. A clinico-pathological correlation in 65 cases. *Br Heart J* 1969; **31**: 206–18.
5 Kay HB. Ventricular complexes in heart block. *Br Heart J* 1948; **10**: 177–87.
6 Penton GB, Miller H, Levine SA. Some clinical features of complete heart block. *Circulation* 1956; **13**: 801–24.
7 Wright JC, Hejtmancik MR, Herrmann GR, Shields AH. A clinical study of complete heart block. *Am Heart J* 1956; **52**: 369–87.
8 Rowe JC, White PD. Complete heart block: a follow-up study. *Ann Intern Med* 1958; **49**: 260–70.
9 Friedberg CK, Donoso E, Stein WG. Non-surgical acquired heart block. *Ann NY Acad Sci* 1964; **III**: 835–47.
10 Chatterjee K, Harris A, Davies G, Leatham A. Electrocardiographic changes subsequent to artificial ventricular depolarisation. *Br Heart J* 1969; **31**: 770–9.
11 Davies MJ. *Pathology of the conducting tissue of the heart*. London: Butterworths, 1971.
12 Siddons H. Deaths in long-term paced patients. *Br Heart J* 1974; **36**: 1201–9.
13 Swanton RH, Brooksby IAB, Jenkins BS, *et al.* Determinants of angina in aortic stenosis and the importance of coronary arteriography. *Br Heart J* 1977; **39**: 1347–52.
14 James TN, Burch GE. Blood supply of the human inter-ventricular septum. *Circulation* 1958; **17**: 391–6.
15 Romhilt DW, Hackel DB, Estes EH Jr. Origin of blood supply to sinoauricular and atrioventricular node. *Am Heart J* 1968; **75**: 279–80.

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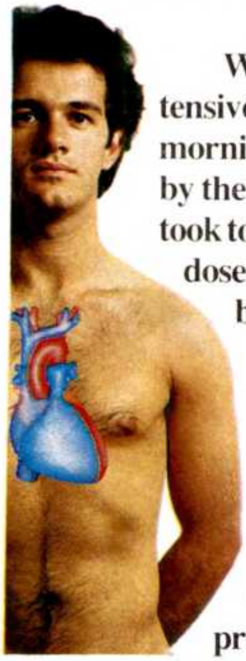

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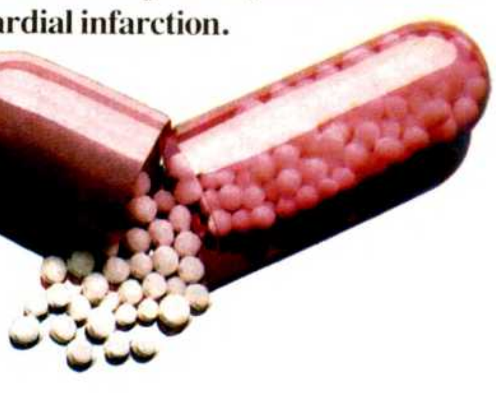

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Assessment of left ventricular contractility during supine exercise in children with left-sided cardiac disease

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SUMMARY Exercise stresses the cardiovascular system and causes it to use its reserve capacities. Exercise assessment may unmask abnormalities of left ventricular contractility not suspected from or detected by resting measurements. We have studied the following indices of left ventricular contractility in 21 children with left-sided congenital heart disease: maximum dP/dt, Vmax, Vpm, Vcf, and peak meridional wall stress. Studies were performed in the supine posture at rest, and at 25 per cent, and 50 per cent of a predetermined maximal upright workload on a bicycle ergometer. The method of measurement used simultaneous high fidelity catheter pressure tracings and M-mode echocardiography. There were no complications and the technique appeared practical and safe. The measurements of contractility differentiated patients with left ventricular volume or pressure overload from each other and from patients with either volume plus pressure overload, or myocardial dysfunction. These measurements can be used to measure the functional reserve capacity of patients with left-sided lesions, and may be useful in follow-up studies, especially before and after operation.

Adult studies have shown that exercise may unmask abnormalities of left ventricular contractility not detected at rest.[1 2] No such information exists for children. There are few data concerning the assessment of left ventricular contractility at rest in normal children, and in those with congenital heart disease.[3–6] Computer analysis of high-fidelity catheter pressures readily allows measurement of indices of contractility, such as maximum dP/dt, Vmax, and Vpm, the normal resting values of which in children have been published.[3–5] By combining the pressure tracing with a simultaneous M-mode echocardiogram measuring left ventricular volumes, Vcf and peak meridional wall stress may also be calculated.[7 8] These indices may be used during exercise to assess the reserve capacity of patients' ventricular functional performance. Though the use of indices of contractility has been questioned,[9] proponents of other methods of assessment have failed to show any superiority for their techniques.

The purpose of this study was to evaluate the feasibility, safety, and potential value of measuring in this way indices of left ventricular contractility, that is, maximum dP/dt, Vmax, Vpm, Vcf, and peak meridional wall stress, during supine cycle ergometer exercise in children with left-sided cardiac disease, using this combination of M mode echocardiogram and high fidelity pressure tracings.

Patients and methods

Patients were selected from those admitted for routine cardiac catheterisation. The procedure was approved by the Committee on Human Experimentation, The Hospital for Sick Children, and the University of Toronto. Informed written consent was obtained either from the parents or the patient. Patients were included if they were over 7 years of age and had left-sided pressure or volume overload or cardiomyopathy, but had no left-to-right shunt. Twenty-one patients completed the procedure (Table). The haemodynamic or functional abnormalities were as follows: left ventricular pressure overload group (n=13), left ventricular volume overload group (n=3); left ventricular pressure

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plus volume overload group (n=3); congestive cardiomyopathy (n=1); previous resection of a left ventricular outflow tract obstruction with no residual gradient (n=1).

Table *Clinical data*

Group		*Case no.*	*Age (y)*		*Diagnosis*
			Mean	*Range*	
Pressure overload	a	1–6	13·5	11–16	Aortic valve or subvalve stenosis; trivial or no aortic regurgitation
	b	7–13	12·6	10–17	Coarctation of aorta
Volume overload	a	14, 15	15·0	14–16	Aortic regurgitation; systolic gradient across aortic valve < 20 mmHg
	b	16	14	—	Mitral regurgitation
Pressure + volume overload		17–19	12·0	8–18	Aortic stenosis plus significant aortic regurgitation
Cardiomyopathy		20	19	—	Non-obstructive cardiomyopathy
Postoperative		21	12	—	Postoperative subaortic diaphragm resection, no residual systolic gradient

The day before catheterisation, each patient underwent a simple upright progressive stress test on an electronically braked cycle ergometer (model AM368, 368, Elema-Schonander, Stockholm, Sweden) as described by Godfrey *et al.*[10] The maximum upright workload achieved and maintained for one minute (kilogram metres) was used as the basis for the exercise period during catheterisation. The mean workload achieved was 876 (kg m) ±300 (SD) (range 500 to 1400). This workload corresponded to 97 ±15 per cent of that predicted (range 75 to 127 per cent).

On the day of catheterisation the patients were only mildly sedated (meperidine 1·0 to 1·5 mg/kg and diazepam 0·2 to 0·3 mg/kg by mouth) in order to be able to perform ergometer exercise. The right antecubital fossa was anaesthetised with 2 per cent xylocaine and catheters were placed in the median basilic vein by cut-down, and in the right brachial artery by the percutaneous technique. After diagnostic haemodynamic data had been obtained, a high fidelity catheter, zeroed to atmospheric pressure, either a twin sensor (one in left ventricle, one in aorta) or single sensor (left ventricle) was placed in position via the brachial artery (Model PC-761 or PC-350, Millar Instruments, Inc., Houston, Texas). The zero calibration was repeated after pressure measurements were completed to ensure that no drift had occurred.

Echocardiograms were recorded with a hand-held 0·25 or 0·5 in, 5 cm focused, 2·25 MHz transducer (Aerotech, Inc, Lewiston, Pennsylvania) and a Hoffrel Model 101 ultrasonoscope (Hoffrel Instruments, Norwalk, Connecticut), and a Cambridge multichannel recorder (Model 1005, Cambridge Instrument Co, Ossining, New York). The echocardiogram traces during catheterisation were at the level of the left ventricular cavity just below the tips of the mitral valve leaflets. The left ventricular pressure tracing and electrocardiogram were superimposed on the echocardiogram to allow simultaneous analysis of pressure-volume relations (Fig. 1 and 2).

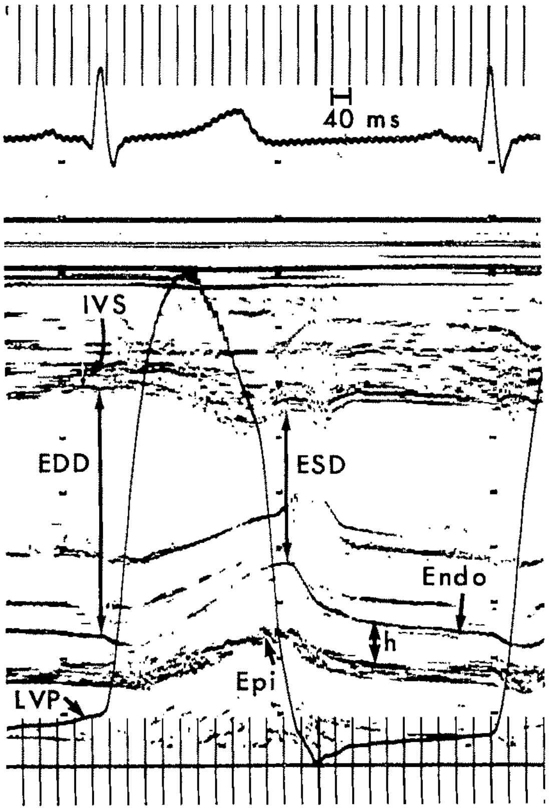

Fig. 1 *Simultaneous M-mode echocardiogram of the left ventricular (LV) cavity, endocardium (endo), and interventricular septum (IVS) with the high-fidelity LV pressure (LVP) superimposed. Arrows show method of measurement of IVS thickness, LV end-diastolic dimension (EDD), end-systolic dimension (ESD), and wall thickness (h). Epi, epicardium.*

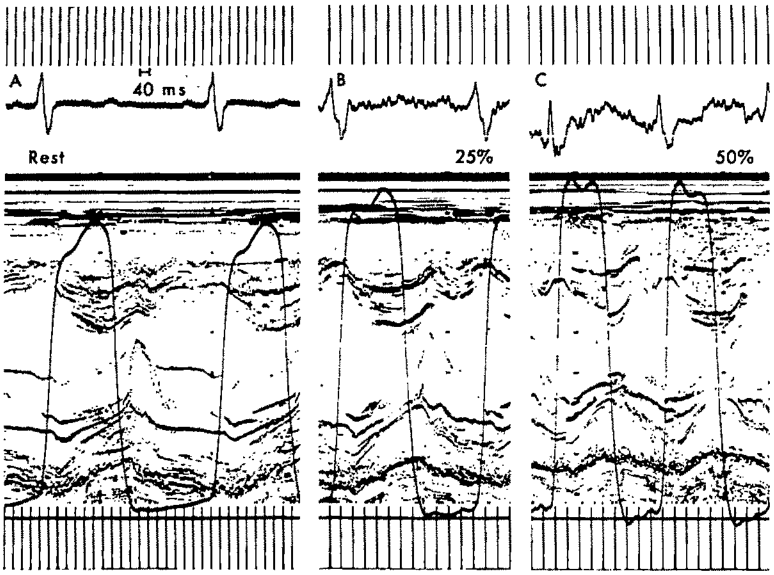

Fig. 2 *Echocardiograms and pressure traces with increasing exercise levels in the same patient: (A) at rest; (B) at 25 per cent maximum workload; (C) at 50 per cent maximum workload. For method of measurement, see Fig. 1.*

The patient was moved to the caudal end of the catheterisation table for supine exercise. After his feet had been raised into the ergometer pedals (approximately 20 cm above the level of the catheterisation table, depending on the size of the patient) for at least three minutes, measurements were carried out at rest. These measurements included the maximum value for the first differential of pressure versus time (left ventricular dP/dt), the peak velocity of muscle shortening (Vpm), and the maximum velocity of the contractile element (Vmax) derived from a Hewlett-Packard catheterisation data analysis system, model 5600. The dP/dt, Vpm, and Vmax values from case 16 (mitral regurgitation) were not included because of the lack of an isovolumic contraction period. The computer system calculated dP/dt by a differentiator with a 16 Hz cutoff. Vmax and Vpm were calculated from derived left ventricular pressures as described by Mirsky *et al.*[11] with K=30.

From the echocardiographic and pressure recordings, the mean velocity of circumferential fibre shortening (Vcf) and peak meridional wall stress were calculated. The echocardiographic Vcf was calculated as follows:

$$\frac{\text{LVEDD} - \text{LVESD}}{\text{LVEDD} \times \text{LVET}}$$

where LVEDD=left ventricular end-diastolic dimension, LVESD=left ventricular end-systolic dimension, and LVET=left ventricular ejection time.

The left ventricular ejection time was obtained by computer by simultaneous analysis of heart rate, left ventricular pressure, and aortic pressure. The peak value for meridional wall stress was obtained from the following equation:

meridional wall stress

$$= \frac{\text{LV pressure} \times \text{LV dimension}}{4\text{h } (1 + \text{h/dimension})} \times 10^3 \text{ dynes/cm}^2,$$

where h=left ventricular endocardial thickness. The necessary variables were measured at 40 ms intervals and wall stress was calculated; the largest value was equated with peak meridional wall stress.

After the data for each of the above indices had been obtained, the patient began to pedal at 60 revolutions per minute at a workload approximately 25 per cent of the previous day's maximum upright workload. Because of technical limitations, this workload was the nearest 50 kg m multiple. After two and a half minutes were allowed for the achievement of a steady state, the variables were recorded again. After satisfactory data had been collected, the workload was increased to 50 per cent of the maximum upright workload and after two and a half minutes the variables were measured for a third time. After completion of the exercise studies, the patient returned to the cranial end of the catheterisation table for angiography.

STATISTICAL ANALYSIS

Data were evaluated within clinical groups by analysis of variance. If variance ratios were not unequal, then P values were obtained by either paired or unpaired Student's t test. The data shown in the figures are mean values; no rigorous comparison of variables between groups was made because of the small numbers of patients.

Results

MAXIMUM DP/DT

The values for maximum dP/dt at rest (Fig. 3) showed a small separation, which reflected the patients' haemodynamic abnormalities. The patients with left ventricular pressure overload and pressure plus volume overload had the highest values, while those with left ventricular volume overload and muscle dysfunction had lower values. The responses to exercise showed further separation than at rest. The rise from rest to 25 per cent maximal upright workload and from 25 to 50 per cent was significant ($p < 0{\cdot}01$) in both the patients with aortic stenosis and those with coarctation.

To allow for differing initial values, the percentage changes from resting measurements were calculated (Fig. 4). The patient with cardiomyopathy (case 20) showed only a small increase from the resting to the 25 per cent level; all other patients had larger increases. At the 50 per cent level, the same case showed a decrease to below the resting value, whereas other patients showed an increase of at least 65 per cent above it.

VPM

The resting values for Vpm (Fig. 3) were closely grouped. As the exercise level increased there was a wider separation of values, with the increases in the aortic stenosis and coarctation groups significant at the $p < 0{\cdot}02$ and $p < 0{\cdot}001$ level, respectively, for the interval from rest to 25 per cent of maximum upright workload. The small number of values for the 50 per cent level precluded their analysis. Again, patients with left ventricular pressure overload showed the highest values. Analysis by percentage changes from baseline (rest) values (Fig. 4) appeared to increase the separation obtained. The left ventricular volume overload and volume and pressure overload groups, however, had changed places in comparison with their curves of maximum dP/dt.

VMAX

As with the previous two indices, values at rest (Fig. 3) were too close to separate the various

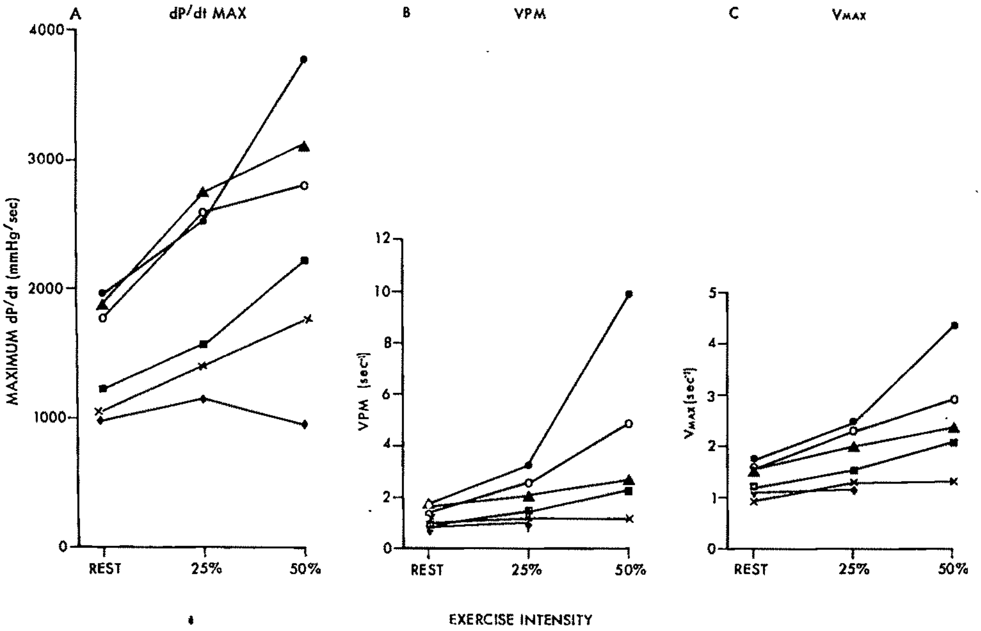

Fig. 3 *LV pressure-derived indices of contractility with increasing exercise levels: (A) maximum dP/dt (mmHg/s); (B) VPM (s^{-1}); (C) Vmax (s^{-1}). Clinical groups of patients represented by the following symbols: Circles, pressure overload:* ●, *aortic stenosis;* ○, *coarctation; squares, volume overload:* ■, *aortic regurgitation;* ▲, *volume plus pressure overload;* ◆, *cardiomyopathy;* ×, *postoperative resection.*

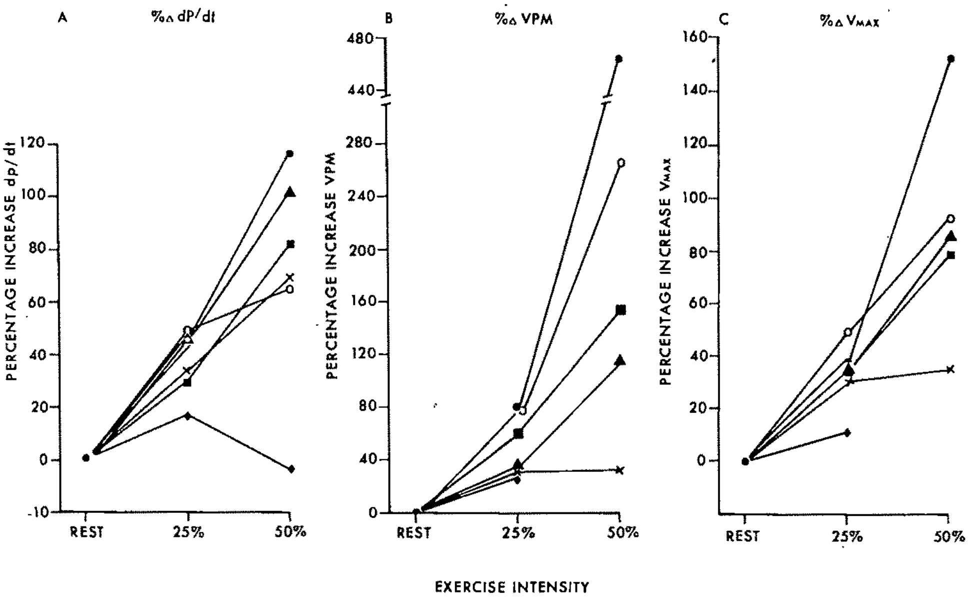

Fig. 4 *Percentage changes (%Δ) from resting values for LV pressure-derived indices of contractility with increasing exercise intensity: (A) maximum dP/dt; (B) VPM; (C) Vmax. Symbols as in Fig. 3.*

haemodynamic groups reliably. The increase from rest to 25 per cent of maximum upright workload was significant in both pressure overload groups (p < 0·01 (aortic stenosis) and p < 0·001 (coarctation)). The rise in the intensity of exercise led to the same pattern of values as with Vpm. The patients with left ventricular pressure overload had the highest values; those with combined pressure plus volume overload intermediate values, and those with left ventricular volume overload or muscle dysfunction the lowest values. The percentage change plot (Fig. 4) failed to add further specificity.

VCF

The values from all patients except case 20 showed almost linear responses with increasing exercise levels (Fig. 5). The patient with cardiomyopathy (case 20) showed a transient increase, followed by a fall below baseline at the 50 per cent level. This pattern was similiar to his data for dP/dt.

The patient with mitral regurgitation, whose values for Vpm, dP/dt, and Vmax could not be included because of the lack of an isovolumic contraction period, had a Vcf response which closely resembled the two other patients with left ventricular volume overload.

PEAK MERIDIONAL WALL STRESS

The values of peak meridional wall stress (Fig. 5) varied widely at rest, but at 50 per cent of maximal upright workload, the patients within subgroups became very similar. The patients with pressure overload maintained relatively low values for peak wall stress with increasing exercise intensity, while those with left ventricular volume overload con-

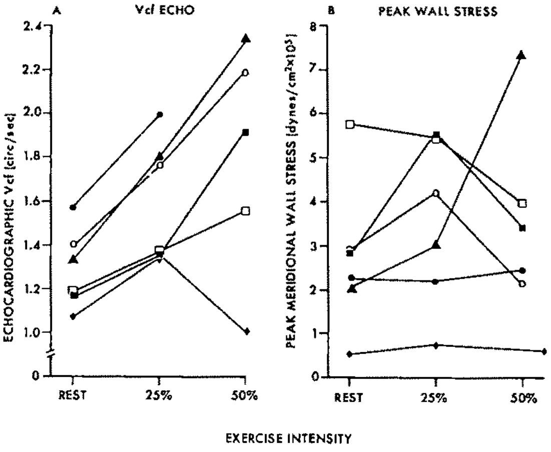

Fig. 5 *Echocardiographic and LV pressure-derived indices of contractility plotted against increasing exercise levels: (A) Vcf (circ/s); (B) peak meridional wall stress (dynes/cm² × 10⁵). Symbols as in Fig. 3, with the addition of □, the patient with mitral regurgitation.*

sistently maintained higher levels of peak wall stress. The combination of left ventricular pressure and volume overload did not give intermediate values as with Vmax, Vpm, and maximum dP/dt, the haemodynamic disturbances appearing to be additive, giving this group the highest values of peak wall stress. The large increase in this group occurred in association with increased left ventricular end-diastolic pressure, and decreased oxygen supply : demand ratio. The myocardium in case 20 maintained low peak wall stress values. This was associated with an unchanged systolic blood pressure and lower than expected cardiac output with exercise.

Discussion

The purpose of this study was to investigate the feasibility, safety, and potential value of a combined high-fidelity catheter and echocardiographic technique to assess left ventricular contractility during supine ergometer exercise in children with left-sided cardiac lesions. This was carried out in 21 patients, in none of whom were there complications related to the presence of the catheter in the left ventricle during exercise. While the number of patients is still small, the technique appears safe, and may provide valuable additional information which will be helpful in the assessment of the functional reserve capacity of the left ventricle in children either before or after operation.

CONTRACTILITY INDICES AT REST: MAXIMUM DP/DT, VPM, VMAX

There are few data available concerning left ventricular contractility indices in children with congenital heart disease. Graham *et al.*[3] established normal values for maximum dP/dt, Vpm, and Vmax. Jarmakani *et al.*[4] extended the use of these indices to patients with successfully corrected ventricular septal defects. The theoretical assumptions that must be made in order to calculate these variables include: (1) that an isovolumic contraction period exists, (2) that left ventricular geometry does not change during this contraction, and (3) that there is relative independence of these variables from preload and afterload. In our study, we did not include the values for dP/dt, Vpm, and Vmax in a patient with mitral regurgitation because of the lack of a true isovolumic contraction period. For the same reason, patients with aortic regurgitation might also be excluded, but it has been suggested that contractility indices are valid unless aortic regurgitation is severe[12] and in support of this, in our patients with this lesion, angiographic regurgitation diminished considerably near end-diastole, and probably was minimal during the initial phase of contraction. In contrast, the indices Vpm and peak wall stress do not depend on an isovolumic contraction period, but are still dependent on geometric considerations.[8]

The normal value for maximum dP/dt is 1410 ±50 mmHg/s.[4] Our patients with pressure overload and pressure plus volume overload had values higher than this (Fig. 3). The dP/dt values in the left ventricular volume overload group and in cases 20 and 21 were below normal, similar to Jarmakani's patients with ventricular septal defect and unobstructed right ventricular outflow. Our findings may confirm Jarmakani's suggestion that the volume-overloaded left ventricle has impaired contractility.

The normal value for Vpm,[4] 1·30 ±0·05/s, was exceeded at rest by the left ventricular pressure and pressure plus volume overload patients (Fig. 3). Again, the patients with volume overload, as well as those with congestive cardiomyopathy (case 20) and postoperative left ventricular outflow obstruction (case 21), had decreased values, in the same range as Jarmakani's patients with volume overload.

The values for Vmax for our patients with pressure overload were at or only slightly above the normal value,[4] 1·50 ±0·09/s, derived from total left ventricular pressure (Fig. 3). The other patients had lower values, similar to the decreases shown for maximum dP/dt and Vpm.

EXERCISE RESPONSES: MAXIMUM DP/DT, VPM, VMAX

There are no data for normal children during exercise for any of the left ventricular indices of contractility measured. Because of the availability of sophisticated non-invasive precatheter assessments, that is M-mode and cross-sectional echocardiography, we have not catheterised any patients with trivial heart disease or none at all.

Our patient with cardiomyopathy had the greatest impairment of left ventricular function of all those studied; his ability to increase contractility in response to supine exercise was limited (Fig. 3 and 4). Previous reports of exercise studies in healthy volunteer adults have shown increases in contractility during isotonic exercise,[13 14] and impairment in contractility in patients with acquired left ventricular dysfunction.[1 2] We might expect that the increases in each of the other groups of patients is the more normal response. Whether, in fact, the patients with pressure overload, many of whom had a hypercontractile angiographic appearance, had exercise values for maximum dP/dt, Vpm, and Vmax which were *above* normal cannot be assessed as yet. In previous studies, patients with left ventricular hypertrophy had impaired contractility at rest[15–17] and this may not persist during isotonic exercise; the added muscle mass may permit higher pressures and flows to occur in response to peripheral demand.

ECHOCARDIOGRAPHIC-DEPENDENT INDICES AT REST: VCF, PMWS

Each group of patients showed a separation of Vcf values consistent with that predicted from their haemodynamics. Vcf, however, has been shown to vary with rate and age.[18 19] A value of 1·34 ± 0·03 circ/s has been considered normal for patients in this age group.[20] Only our patient with cardiomyopathy (Fig. 4) had a value below that (1·07 circ/s). The assumption that changes in contractility are reflected by changes in Vcf can only be valid if the change in heart rate after an intervention has been taken into account. We did not recalculate Vcf values for each patient because heart rates did not differ widely in our patients.

Peak meridional wall stress has been investigated in adults[7 8] but in only a few children.[6] The advantages of using an echocardiographic assessment of peak meridional wall stress include: the absence of the depressive effects of contrast material, the lack of any need to assume the long axis measurement, and the ease with which preoperative and postoperative measurements may be compared, measurements which are not dependent on the placing of epicardial markers. We observed neither eccentric left ventricular hypertrophy nor regional asynergy in any of our patients. There is evidence[8] that peak meridional wall stress may be a more sensitive indicator of ventricular contractility than circumferential wall stress. The reason for this is related to the assumptions concerning ventricular geometry. Circumferential wall stress calculations vary as the left ventricle assumes a more spherical shape with deteriorating function. So far there have been no studies in children on changes in peak meridional wall stress with different congenital heart lesions. There are data from normal children at rest, however. The peak meridional wall stress values in nine patients were $1{\cdot}52 \pm 0{\cdot}47$ dynes/cm$^2 \times 10^5$ (mean ± SD), with a range of 0·8 to 2·31 (Lee Benson, 1979, unpublished observations). The values in our patients at rest (Fig. 5) were either at the upper end of or above the normal range, with the exception of the patient with cardiomyopathy. His wall stress value was low because of low pressures and a slightly enlarged but extremely hypertrophied left ventricle.

EXERCISE RESPONSES: VCF, PMWS

All patients except the one with cardiomyopathy showed almost linear, parallel increases in echocardiographic Vcf with exercise. The patients with left ventricular pressure overload had the highest Vcf values both at rest and with increasing exercise intensity. The patient with cardiomyopathy had a similar increase to the 25 per cent level of maximum upright workload but then an abrupt fall to below the baseline value at the 50 per cent level. This indicates a very poor functional reserve. We are unaware of any exercise Vcf data in normal children with which to compare those from our patients. It seems reasonable to expect that as rate increases, with decreased left ventricular ejection time, slightly smaller ventricular dimensions, and an increased ejection fraction,[13] Vcf would increase, but without normal data, we cannot judge whether these patients with left-sided cardiac abnormalities had a high, low, or normal Vcf response.

With increasing exercise intensity, the peak meridional wall stress values showed considerable variation. The peak exercise peak wall stress values of the patients with left ventricular pressure overload were similar to their resting values, suggesting good functional reserve of left ventricular contractility. The patients with left ventricular volume overload had the highest values at 25 per cent of maximum upright workload, indicative of haemodynamic changes which lead to a larger left ventricular volume overload in the absence of appropriate pressure and wall thickness changes necessary to normalise peak wall stress. The patients with left ventricular volume plus pressure overload had a striking increase in peak meridional wall stress with increasing exercise intensity. The left ventricular end-diastolic pressure rose with exercise and oxygen supply demand ratios of these patients had become abnormal,[21] so that this rise in peak wall stress clearly reflected the impaired left ventricular contractility present during exercise. Since these patients had among the lowest values for resting peak meridional wall stress, exercise unmasked abnormal left ventricular function which could not have been otherwise predicted. The lack of increase in peak meridional wall stress in the patient with cardiomyopathy was unexpected. His left ventricular end-diastolic pressure rose considerably with exercise and each of the other indices studied suggested that his left ventricular contractility was the worst of all of the patients studied. Possibly it was so impaired that the myocardium was unable to respond to peripheral demands and that he incurred a large metabolic debt by the use of anaerobic metabolism.

Conclusions

We have used a combined high-fidelity catheter and echocardiographic technique to assess left ventricular contractility in 21 children during supine exercise which appears to be of potential value in the pre- and postoperative assessment of the functional reserve capacity of the left ventricle of children with left-sided cardiac disease. There were no complications; we consider the technique practical and safe. Because of the relatively few patients within each subgroup and the lack of age-matched controls, the value of it cannot yet be accurately assessed. We were able to unmask responses which deviated from those theoretically expected. The studies were effected by a physiological intervention, that is exercise; no alteration in haemodynamics was introduced by the measuring process itself.

References

1 Mason SJ, Weiss JL, Weisfeldt ML, Garrison JB, Fortuin NJ. Exercise echocardiography: detection of wall motion abnormalities during ischemia. *Circulation* 1979; **59:** 50–9.

2 Bussmann WD, Mayer V, Kober G, Kaltenbach M. Ventricular function at rest, during leg raising and physical exercise before and after aortocoronary bypass surgery. *Am J Cardiol* 1979; **43:** 488–93.

3 Graham TP Jr, Jarmakani JM, Canent RV Jr, Anderson PAW. Evaluation of left ventricular contractile state in childhood. Normal values and observations with a pressure overload. *Circulation* 1971; **44:** 1043–52.

4 Jarmakani JM, Graham TP Jr, Canent RV Jr. Left ventricular contractile state in children with successfully corrected ventricular septal defect. *Circulation* 1972; **45** & **46,** suppl 1: I-102–I-110.

5 Mirsky I, Ellison RC, Hugenholtz PG. Assessment of myocardial contractility in children and young adults from ventricular pressure recordings. *Am J Cardiol* 1971; **27:** 359–67.

6 Benson L, Bloom K, Williams C, Olley P, Rowe R. Echographic and hemodynamic evaluation of left ventricular function in children (abstract). *Am J Cardiol* 1979; **43:** 365.

7 Brodie BR, McLaurin LP, Grossman W. Combined hemodynamic-ultrasonic method for studying left ventricular wall stress. Comparison with angiography. *Am J Cardiol* 1976; **37:** 864–70.

8 Gould KL, Lipscomb K, Hamilton GW, Kennedy JW. Relation of left ventricular shape, function and wall-stress in man. *Am J Cardiol* 1974; **34:** 627–34.

9 Elzinga G, Westerhof N. How to quantify pump function of the heart. The value of variables derived from measurements on isolated muscle. *Circ Res* 1979; **44:** 303–8.

10 Godfrey S, Davis CTM, Wozniak E, Barnes CA. Cardiorespiratory response to exercise in normal children. *Clin Sci Mol Med* 1971; **40:** 419–31.

11 Mirsky I, Dhanjoo N, Sandler H. *Cardiac mechanics: physiological, clinical and mathematical considerations.* New York: John Wiley, 1974: 87–112 & 293–329.

12 Yang SS, Bentivoglio LG, Maranthao V, Goldberg H. Assessment of ventricular function. In: *From cardiac catheterization data to hemodynamic parameters.* Philadelphia: F A Davis, 1978: 284–5.

13 Mitchell JH. Mechanisms of adaption of the left ventricle to muscular exercise. *Pediatrics* 1963; **32:** 660–70.

14 Sarnoff SJ, Mitchell JH, Gilmore JP, Remensnyder JP. Homometric autoregulation in the heart. *Circ Res* 1960; **8:** 1077–91.

15 Rackley CE. Quantitative evaluation of left ventricular function by radiographic techniques. *Circulation* 1976; **54:** 862–79.

16 Gunther S, Grossman W. Determinants of ventricular function in pressure-overload hypertrophy in man. *Circulation* 1979; **59:** 679–88.

17 Krayenbeuhl HP, Rutishauser W, Wirz P, Amende I, Mehmel H. High-fidelity left ventricular pressure measurements for the assessment of cardiac contractility in man. *Am J Cardiol* 1973; **31:** 415–27.

18 Fisher EA, DuBrow IW, Hastreiter AR. Comparison of ejection phase indices of left ventricular performance in infants and children. *Circulation* 1975; **52:** 916–25.

19 Gutgesell HP, Paquet M, Duff DF, McNamara DG. Evaluation of left ventricular size and function by echocardiography. Results in normal children. *Circulation* 1977; **56:** 457–62.

20 Goldberg SJ, Allen HD, Sahn DJ. *Pediatric and adolescent echocardiography.* Chicago: Year Book Medical Publishers, 1975: 65.

21 Hoffman JIE. Determinants and prediction of transmural myocardial perfusion. *Circulation* 1978; **58:** 381–91.

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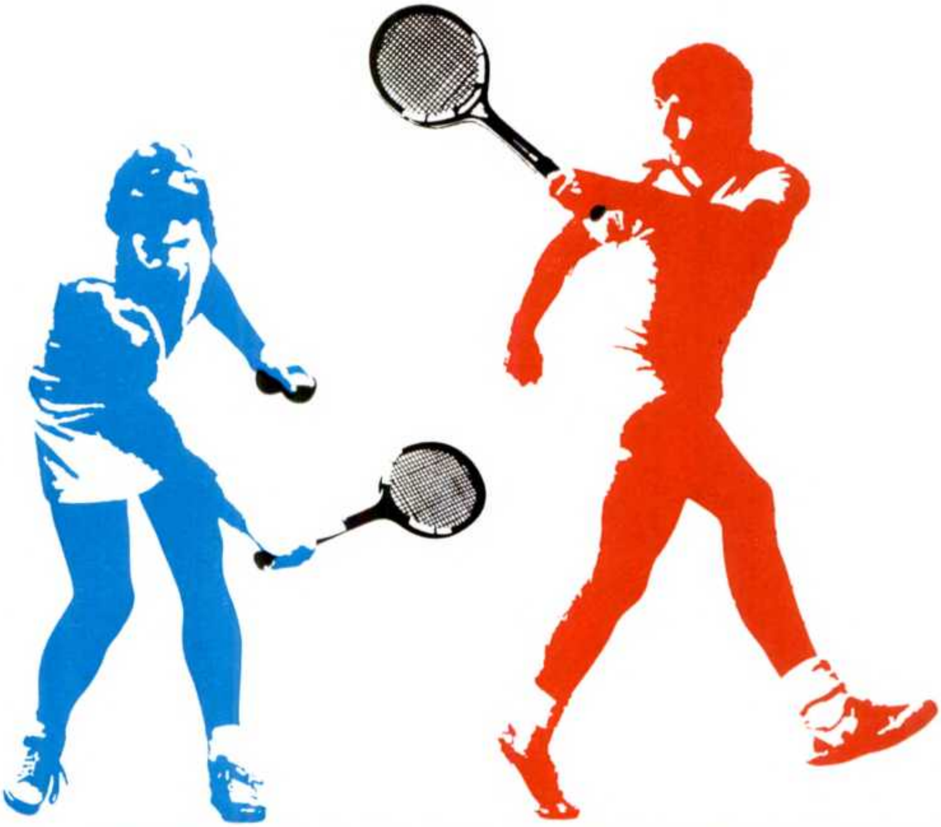

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References

1. Nayler, W.G. *Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
2. Flameng, W. *et al. Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
3. Detry, J.M.R. *et al. Eur. J. Cardiol.* **4,** 165, 1976.
4. Gobel, F.L. *et al. Am. J. Cardiol.* **37,** 139, 1976.
5. Jenkins, M.D. *et al. Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
6. Bloem, Th. J.J.M. *et al. Clin. Cardiol.* **2,** 407, 1979.
7. Shapiro, W. *Proc. Roy. Soc. Med.*, Suppl. (in press 1980).
8. Nordstrom, L.A. *Chest*, **74,** 50, 1978.

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Br Heart J 1980 **44:** 711–3

Aortic atresia occurring with complete transposition of great arteries*

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SUMMARY Aortic atresia occurring with complete transposition of the great arteries (ventriculoarterial discordance) has not previously been reported. A patient with this condition is described, who is alive and relatively well at the age of 6 years. This survival contrasts conspicuously with that of patients with the far commoner situation of aortic atresia with normally connected great arteries. It is suggested that this difference in longevity is a result of the greater ability of the left ventricle to supply both the systemic and pulmonary circulations.

Case report

A female Caucasian infant, weighing 3·5 kg, was born by normal delivery after an uneventful pregnancy to non-consanguineous parents on 9 May 1973. Her neonatal progress was unremarkable and no abnormality was noted until the age of 14 months, when a murmur and mild cyanosis were discovered at routine examination. The child was referred for cardiac catheterisation, underwent two inconclusive investigations, and was started on digoxin and frusemide for mild cardiac failure. At the age of 4 years, she was seen at The Hospital for Sick Children. She was complaining of mild exertional dyspnoea and sweating, but otherwise led a relatively normal life, attending normal school. Developmental milestones were normal. On examination, she was below the third centile for height and weight. She was mildly cyanosed and not dyspnoeic at rest. Her heart rate was 140/min and regular. There was no clubbing. The peripheral pulses were of normal volume and synchronous. The jugular venous pulse was elevated with a prominent "a" wave. The anteroposterior diameter of the chest was much increased. The apex beat was to the right and a systolic thrill was palpable at the right sternal border. An ejection systolic murmur and a mid-diastolic flow murmur were audible maximally in the 3rd right intercostal space. The 2nd heart sound was single. There was 4 cm hepatomegaly and the lungs were clear.

INVESTIGATIONS

The chest *x*-ray film and bronchial tomography disclosed situs solitus of the atria and viscera, a grossly enlarged heart shadow mainly on the right, and increased pulmonary vascularity.

The electrocardiogram showed a normal P wave axis, with right atrial hypertrophy, left ventricular hypertrophy, and interventricular conduction delay.

Table *Haemodynamic data*

Site	*Pressure (mmHg)*	*Mean pressure (mmHg)*	*Oxygen saturation* (%)
Superior vena cava			70
High right atrium	a 28	17	69
Mid right atrium	v 20		62
Low right atrium			67
Inferior vena cava			58
Right ventricle	230/20		
Pulmonary vein			95
Left atrium	a 25		
	v 15	13	
Left ventricle	75/8		90
Ascending aorta	70/50	60	90
Descending aorta	80/50	70	88

Qp = 17·5 l/min per m^2
Qs = 7·3 l/min per m^2
PVR = 2·1 units m^2
SVR = 7·6 units m^2.

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*This work was supported in part by a grant from the British Heart Foundation.

†F J Macartney is supported by the Vandervell Trust and the British Heart Foundation.

The mean frontal QRS axis was indeterminable with a clockwise loop.

The blood haemoglobin concentration was 13·4 g/dl. Cardiac catheterisation and angiocardiography was carried out. The haemodynamic data are recorded in the Table and demonstrate pulmonary hypertension, pressure in the right ventricle above the systemic, a right-to-left shunt at atrial level, and mild systemic arterial desaturation.

Angiocardiography was performed in both

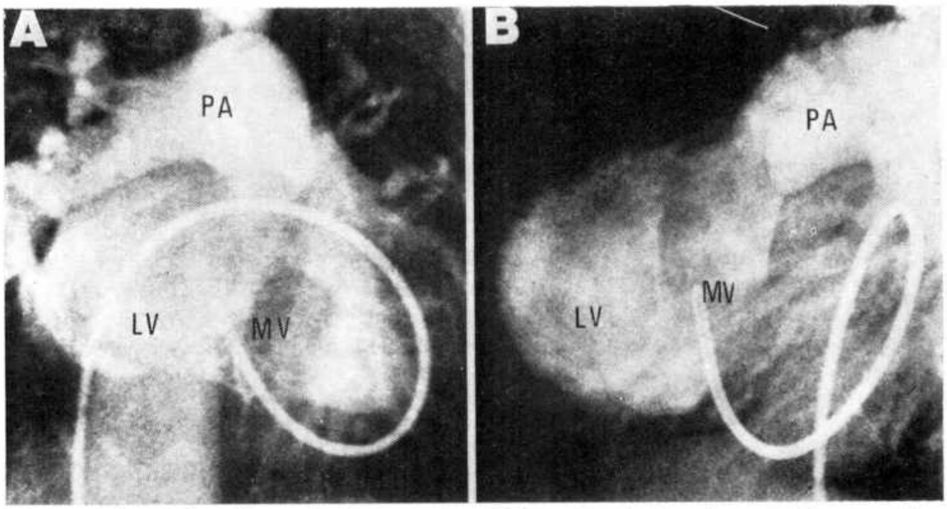

Fig. 1 *Left ventricular angiocardiogram in* (A) *frontal and* (B) *lateral projections, demonstrating connection of the left atrium to the smooth left ventricle (LV) by the mitral valve (MV). The pulmonary artery (PA) originates from the left ventricle.*

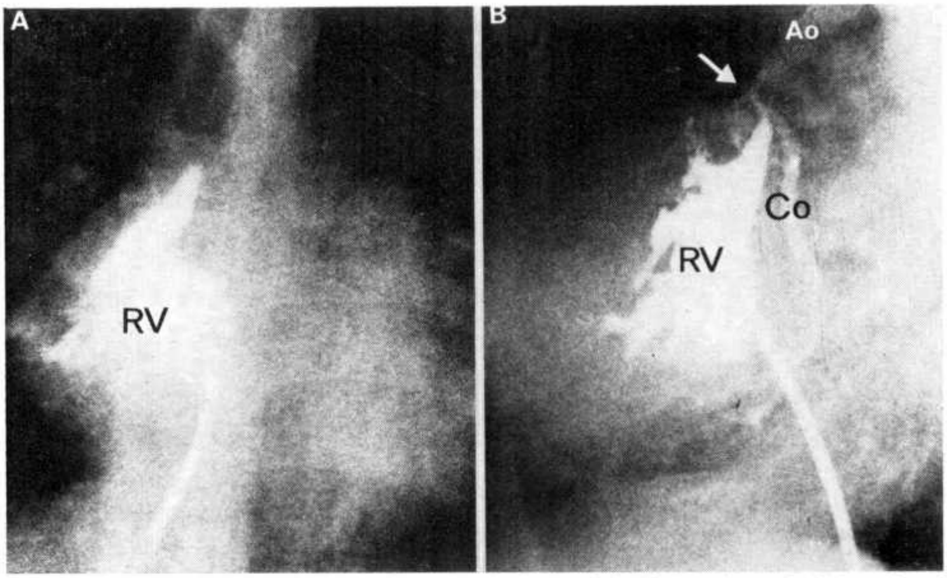

Fig. 2 *Right ventricular angiocardiogram in* (A) *frontal projection, early in the injection and* (B) *lateral projection, later in the injection. The catheter has been advanced from the right atrium through the tricuspid valve. The right ventricle (RV) is heavily trabeculated and hypoplastic. The aortic valve is atretic. However, the circumflex coronary artery (Co) fills from myocardial sinusoids, so that contrast medium passes from the coronary orifice* (white arrow) *to the ascending aorta (Ao).*

ventricles and the ascending aorta through a retrogradely placed catheter. The films showed atrioventricular concordance (Fig. 1 and 2). There was aortic atresia, with the aorta connected to a hypoplastic right ventricle, and the pulmonary artery arising from the left ventricle. A hypoplastic ascending aorta was shown to fill through a large persistent ductus arteriosus. In addition, some opacification of the ascending aorta occurred from the right ventricle, not via the aortic valve, but via myocardial sinusoids communicating with the coronary arteries. The remainder of the systemic circulation was supplied by the descending aorta from the persistent ductus arteriosus.

A variety of surgical approaches was considered, including banding of the pulmonary arteries distal to the persistent ductus arteriosus, but eventually it was felt, in the light of her relatively symptom-free existence, together with the lack of a foreseeable method of complete repair, that surgical palliation was not indicated. Since then she has been followed-up in the outpatients' department and now, at the age of 6 years, remains reasonably well, attending special school. She continues below the third centile for height and weight. Her cardiac failure is moderately well controlled on digoxin therapy alone.

Discussion

The occurrence of aortic atresia in association with complete transposition of the great arteries has not previously been recorded.[1] Our patient is extraordinary also in her continued survival and in the relatively good quality of her life. Survival to 6 years is far in excess of the average age at death which is 13·06 days in the common form of aortic atresia associated with ventriculoarterial concordance.[1] The longest survivor with this more common connection is 3·5 years,[2] though we have recently seen an 11-year-old boy with this condition. Though we cannot exclude the possibility that her survival is simply the result of an unusually large persistent ductus arteriosus and lack of restriction at the atrial septum,[3] one cannot ignore the ventriculoarterial connection. It does appear that the left ventricle in this patient supports the systemic and pulmonary circulation far more effectively than does the right ventricle in typical aortic atresia with ventriculoarterial concordance.

References

[1]Freedom RM. Aortic atresia. In: Keith JD, Rowe RD, Vlad P, eds. *Heart disease in infancy and childhood.* New York: Macmillan, 1978: 542–8.

[2]Moodie DS, Gallen WJ, Griedberg D. Congenital aortic atresia. Report of a long survival and some speculation about surgical approaches. *J Thorac Cardiovasc Surg* 1972; **63:** 726–31.

[3]Saied A, Folger GM Jr. Hypoplastic left heart syndrome. *Am J Cardiol* 1972; **29:** 190–8.

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Premature pulmonary valve opening in a patient with absent tricuspid valve

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SUMMARY Echocardiography (M-mode and cross-sectional) disclosed premature opening of the pulmonary valve (very deep "a" wave) in a young man who underwent tricuspid valvulectomy without valve replacement 32 months before for refractory bacterial endocarditis. Cardiac catheterisation showed a prominent atrial wave on the pulmonary artery pressure curve. Thus, part of the right ventricular ejection appeared to occur before the onset of ventricular systole, as a result of powerful right atrial contraction.

Unusually large "a" waves on the pulmonary valve echo, with failure of the pulmonary cusp to return to its closed position before the onset of ventricular systole, have been described as characteristic of moderate to severe pulmonary valve stenosis.[1] In a young man who had had surgical removal (but not replacement) of his tricuspid valve 32 months previously for bacterial endocarditis which was refractory to medical treatment, M-mode as well as cross-sectional echocardiography disclosed premature opening of the pulmonary valve. A prominent presystolic "a" wave was noted on the pulmonary artery pressure curve.

Case report

A 23-year-old heroin addict presented with high fever in September 1976 caused by bacterial endocarditis (*Streptococcus viridans*) affecting the tricuspid valve. In spite of intensive chemotherapy, he became progressively more febrile and toxic; serial chest *x*-ray showed multiple areas of infarction thought to be caused by successive pulmonary embolisation and echocardiography disclosed large tricuspid valve vegetations. In view of the failure of medical treatment, open heart surgery to excise the infected tricuspid valve was performed; prosthetic valve replacement was not done. The patient made an uneventful recovery and has been living a normal unrestricted life since then, with no symptoms and no limitation of effort tolerance.

On examination (May 1979) prominent jugular venous pulsations and hyperdynamic right ventricular parasternal pulsations were noted. The first heart sound was audible at the apex but not at the left sternal border. No murmur was heard. There was no evidence of congestive heart failure. Right atrial and ventricular enlargement were evident on teleradiography of the chest. The electrocardiogram showed right ventricular hypertrophy.

On M-mode echocardiography (Picker System 80C), the right ventricle appeared dilated and the ventricular septum showed paradoxical (anterior) systolic motion, attributable to right ventricular diastolic overloading. A very large "a" wave was seen on the pulmonary valve echo (Fig. 1) and the cusp did not return to its closed position before the beginning of ventricular systole. Cross-sectional echocardiography, viewing the aortic root and pulmonary artery in short-axis view, confirmed that the pulmonary valve opened before the onset of the QRS complex (Fig. 2).

Right heart catheterisation was performed the day after the echocardiogram was recorded. The right atrial pressure curve was typical of severe tricuspid regurgitation (a=16, v=20 mm, mean=15 mm). The pulmonary artery pressure was normal (peak systolic=22 mm, mean=17 mm), but the pressure tracing showed a prominent "a" wave (18 mm) which followed the onset of the P wave of the electrocardiogram, but preceded the onset of the QRS complex (Fig. 3).

The cardiac output was 6·0 l/min and the cardiac index 2·7 l/min per m² (Fick method). Angiocardiography (right ventricular injection) showed severe tricuspid regurgitation and dilatation of the right atrium and ventricle.

Comment

Very large "a" waves on the pulmonary valve echo, sometimes referred to as premature pulmonary

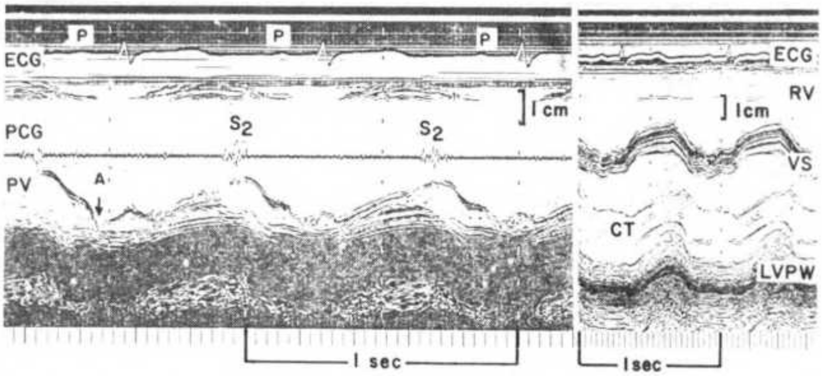

Fig. 1 *M-mode echocardiogram. In the left panel, the pulmonary valve (PV) is seen to open fully after the onset of the P wave (large "a" wave), well before the onset of the QRS. ECG, electrocardiogram; PCG, phonocardiogram; S_2, second heart sound. The right panel shows the left ventricle at chordae tendineae (CT) level. The right ventricle (RV) is dilated and the ventricular septum (VS) shows paradoxical anterior systolic motion. LVPW, left ventricular posterior wall.*

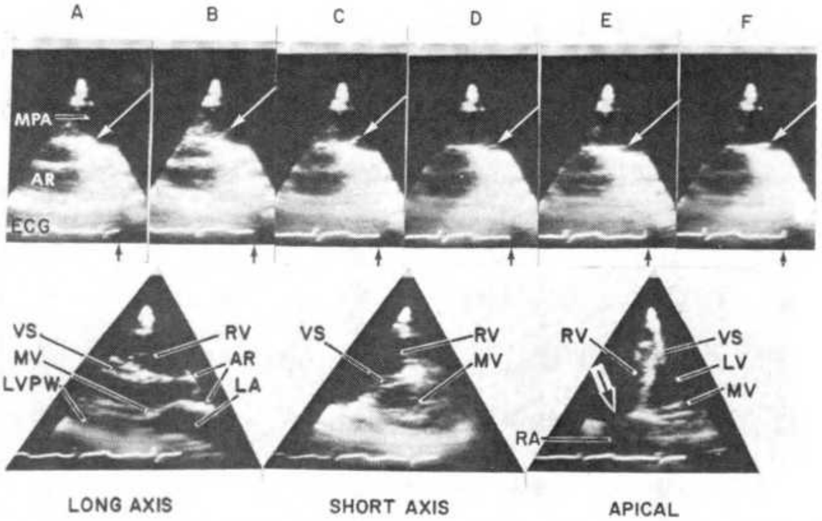

Fig. 2 *Cross-sectional echocardiogram. The upper row of six frames shows the posterior cusp of the pulmonary valve in different phases of the cardiac cycle, which are indicated on the electrocardiogram by the small black upward arrows. The cusp is in an open position in systole* (frame A), *then closes in early to mid-diastole* (B and C), *but opens in late diastole* (D and E) *after onset of the P wave. Frame* F, *during inscription of the S wave, approximates onset of ventricular systole. AR, aortic root; MPA, main pulmonary artery. The lower three frames, in the long axis, short axis, and apical views, respectively, were all taken during systole. They show that the right ventricle (RV) is dilated, while the left ventricle (LV) is of normal size. The arrow in the apical view indicates where the tricuspid valve would have been seen if it was present. VS, ventricular septum; MV, mitral valve; LVPW, left ventricular posterior wall; LA, left atrium; RA, right atrium.*

valve opening, are considered an important sign of moderate to severe pulmonary valve stenosis.[1] This finding has also been noted in a patient with aorta-right atrial fistula resulting from rupture of a sinus of Valsalva aneurysm,[2] in a patient with Uhl's anomaly of the right ventricle,[3] in a patient with pulmonary regurgitation and right ventricular outflow obstruction,[4] and also occasionally in constructive pericarditis.[5]

Haemodynamic factors predisposing to "atriogenic" pulmonary valve opening (that is valve opening before the onset of ventricular systole), include high right ventricular diastolic pressure and unusually forceful right atrial contraction. In our patient, there is evidence that these two factors are present.

The presystolic prominent "a" wave on the pulmonary artery pressure curve is an interesting feature which has hitherto not been reported, to our knowledge, except in a patient with Uhl's anomaly.[3] It is attributable to unusually strong contraction of the right atrium, which in turn may result from diastolic overload of this chamber (Starling's law). Chronic massive tricuspid regurgitation, in our patient, could have produced atrial hypertrophy.

Feigenbaum[5] mentioned having "noted premature opening of the pulmonic valve in patients with tricuspid insufficiency and right heart failure", but added "the pulmonic valve presumably opens following rapid rise in right ventricular pressure in early diastole that occurs in these conditions". In another report from Feigenbaum's laboratory, Wann *et al.*[6] reported five cases of premature pulmonary valve opening, detected by M-mode echocardiography, three of whom had tricuspid regurgitation. The authors concluded that, in all their patients, "alterations in right ventricular diastolic pressure relative to pulmonary artery diastolic pressure account for opening of the pulmonary valve without the contribution of atrial or ventricular systole".

That surgical removal of the tricuspid valve is compatible with life and even the absence of severe cardiac symptoms has been well documented,[7,8] though these authors did not include echocardiographic data in their reports.

One of the compensatory mechanisms enabling the right heart to cope with the burden of massive tricuspid regurgitation is the increased diastolic stretch of right ventricular and right atrial myocardium (Starling's law). Another mechanism, demonstrated in our case, is the ability of the right atrium to shoulder part of the right heart diastolic overload by ejecting part of the right heart stroke output into the pulmonary artery, even before the right ventricle begins to contract.

This patient was operated on by Dr C E Anagnostopoulos.

References

1 Weyman AE, Dillon JC, Feigenbaum H, Chang S. Echocardiographic patterns of pulmonic valve motion in valvular pulmonary stenosis. *Am J Cardiol* 1974; **34:** 644–51.

2 Weyman AE, Dillon JC, Feigenbaum H, Chang S. Premature pulmonic valve opening following sinus of Valsalva aneurysm rupture into the right atrium. *Circulation* 1975; **51:** 556–60.

3 French JW, Baum D, Popp RL. Echocardiographic findings in Uhl's anomaly. *Am J Cardiol* 1975; **36:** 349–53.

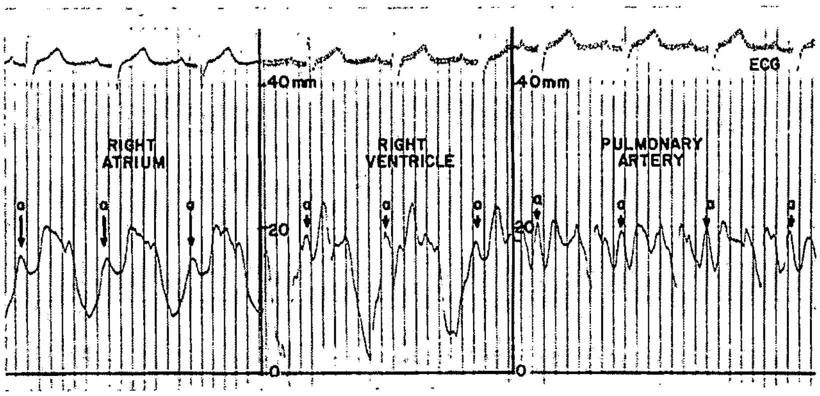

Fig. 3 *Pressure tracings obtained during right heart catheterisation. The right atrial and right ventricular pressure curves are similar and show a large regurgitant "v" wave, preceded by a prominent "a" wave. Note the unusual finding of an "a" wave on the pulmonary artery pressure curve.*

4 Weyman AE, Dillon JC, Feigenbaum H, Chang S. Pulmonary valve echo motion in pulmonary regurgitation. *Br Heart J* 1975; **37:** 1184–90.

5 Feigenbaum H. *Echocardiography*. Philadelphia: Lea & Febiger, 1976.

6 Wann LS, Weyman AE, Dillon JC, Feigenbaum H. Premature pulmonary valve opening. *Circulation* 1977; **55:** 128–33.

7 Robin E, Thoms NW, Arbulu A, Ganguly SN, Magnisalis K. Hemodynamic consequences of total removal of the tricuspid valve without prosthetic replacement. *Am J Cardiol* 1975; **35:** 581–6.

8 Sethia B, Williams BT. Tricuspid valve excision without replacement in a case of endocarditis secondary to drug abuse. *Br Heart J* 1978; **40:** 579–80.

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Use of contrast echocardiography in diagnosis of anomalous connection of right superior vena cava to left atrium

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SUMMARY A 4-month-old infant with cyanosis but without other abnormal cardiac findings is presented in whom the diagnosis of anomalous systemic venous connection to the left atrium was made by contrast echocardiography. The diagnosis was later confirmed by cardiac catheterisation and selective cineangiography. When saline was injected into a vein on the dorsum of each hand while echocardiographically recording the cardiac structures, the left atrium, left ventricle, and aorta were opacified without visualisation of the right ventricle. Similar study with injection into the right foot produced opacification of the right ventricle without visualisation of the left-sided structures. These data suggested normal drainage of the inferior vena cava with anomalous connection of the superior vena cava to the left atrium.

A review of the previously reported cases of anomalous connection of the right superior vena cava to the left atrium is presented together with the possible embryological origin of this anomaly.

Since the original description of Gramiak and Shah,[1] contrast echocardiography has been used to validate echocardiographic identification of cardiovascular structures,[2 3] to detect left-to-right or right-to-left shunts[4–9] or valvar regurgitation,[4 5] and to diagnose a variety of congenital heart defects.[4 5 9–12] We have used this technique with peripheral vein saline injection[6 9] to diagnose a unique case of systemic venous connection to the left atrium which was later confirmed by cardiac catheterisation and selective cineangiography. The purpose of this report is to illustrate the usefulness of contrast echocardiography in the diagnosis of anomalous systemic venous connection to the left atrium and to present the details of this rare anomaly. Review of the previously reported cases of this anomaly and a hypothesis of its embryological development will also be presented.

Case report

A 4-month-old asymptomatic female infant, the product of a full-term normal pregnancy, labour, and delivery, was found to have moderate cyanosis by the paediatrician. After confirming low arterial Po_2 (31 torr in room air) the infant was referred for further evaluation. Physical examination was completely normal with the exception of moderate central cyanosis. The electrocardiogram was normal. Chest *x*-ray films showed a prominent thymic shadow and questionable mildly decreased pulmonary vascular markings. Her haemoglobin was 13·6 g/100 ml and haematocrit 41 per cent. M-mode echocardiogram was interpreted as normal. Right radial artery Po_2 was 32 torr in FIO_2 of 0·21 and the acid base status was normal. These remained unchanged in FIO_2 of 1·0 for 15 minutes.

Echocardiograms were performed by standard techniques using an Irex Continutrace echocardiograph with a 3·5 MHz focused transducer.[13 14] With the patient in the supine position, the transducer was positioned along the left sternal border in the fourth intercostal space. Recordings of left ventricular cavity (with the right ventricle anterior to it) and aortic root (with the left atrium behind it and right ventricular outflow tract in front of it) were successively made while injecting 1·0 to 1·5 ml normal saline through 25 gauge scalp vein needles inserted into veins of the right and left hands and right foot. These contrast echocardiograms were performed in duplicate. With injection into either hand, the left atrium and aorta were opacified without the appearance of contrast echoes in the right ventricular outflow tract (Fig. 1 A and C).

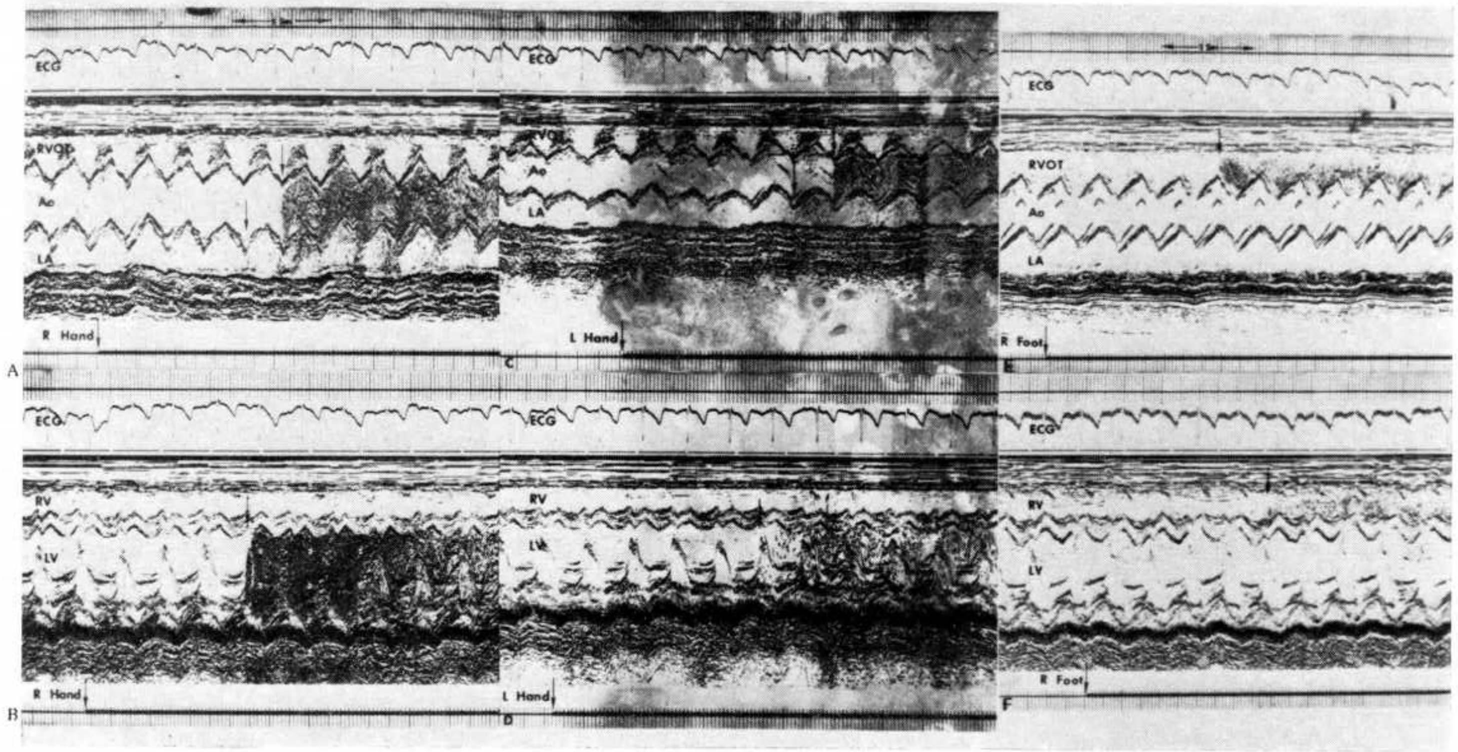

Fig. 1 *While recording the right ventricular outflow tract (RVOT), aorta (Ao), and left atrium (LA) by M-mode echocardiography (A and C), saline, 1 to 1·5 ml, was injected into the veins of right (R) or left (L) hands. The injection is marked by the arrows. Note the appearance of contrast echoes in the left atrium first* (arrows) *and in the aorta* (arrows) *in the next cardiac cycle. Note that the right ventricular outflow tract is free of contrast echoes. Similar injections were made while recording (B and D) the left ventricle (LV) and right ventricle(RV). Note the contrast opacification of the LV* (arrows) *without appearance of contrast echoes in the right ventricle (RV). While echocardiograms similar to the preceding were being obtained, saline was injected in the right foot. Note the opacification of RVOT (E) and RV (F) without contrast echoes in LA, Ao, or LV. The time is marked. ECG, electrocardiogram.*

Similarly, the contrast echoes appeared in the left ventricle without opacification of the right ventricle (Fig. 1 B and D). When saline was injected into a vein of the right foot, the right ventricular outflow tract and right ventricle were, respectively, opacified without opacification of the left atrium, aorta, or left ventricle (Fig. 1 E and F). These data suggest venous drainage of both arms into the left atrium while the inferior vena cava drains normally.

The infant was observed over the next few months and, though she remained asymptomatic, a gradual increase in haemoglobin was observed (Hb 15·0 g/100 ml at the age of 8 months).

Cardiac catheterisation with selective cineangiography was performed at the age of 8 months. There was minimal systemic venous oxygen desaturation without any step-up in O_2 saturations in the right heart (Table 1). The catheter could not be advanced into the superior vena cava from the right atrium. The catheter could be advanced, however, though with difficulty, into the left atrium via a patent foramen ovale and from there into the superior vena cava and both right and left innominate veins. The pulmonary venous oxygen saturation was normal and there was a severe step-down in the O_2 saturation at the left atrial level with the resultant moderate systemic arterial desaturation. The right and left heart pressures were within normal limits (Table 1).

An angiogram was performed with the catheter tip positioned in the right innominate vein. The right superior vena cava (into which the left innominate vein also emptied) was opacified first and was then seen to enter the left atrium (Fig. 2 A and B). The left ventricle and the aorta were subsequently filled in a normal manner. A left innominate vein angiogram excluded the possibility of a persistent left superior vena cava entering the left atrium (Fig. 2 C). Selective left atrial angiography showed retrograde opacification of the right-sided superior vena cava for a short distance but there was no evidence for a persistent left superior vena cava. Thus, the data from the catheterisation and angiography confirmed the diagnosis made with the contrast echocardiography. Because of lack of symptoms and only mild polycythaemia (haemoglbin of 15·0 g/100 ml at the time of the catheterisation) surgical correction of the defect is deferred for the present but is planned for some time in the future.

Table 1 *Cardiac catheterisation data*

Site	*O_2 saturation (%)*	*Pressure (mmHg)*
Superior vena cava	60	a = 6, v = 8, m = 7
Inferior vena cava	62	—
Right atrium	62	a = 4, v = 3, m = 4
Right ventricle	60	23/4
Main pulmonary artery	60	21/14, m = 16
Pulmonary veins (right and left)	98	—
Left atrium	79	a = 7, v = 8, m = 7
Left ventricle	79	75/6
Qp:Qs	0·5:1·0	

Discussion

CONTRAST ECHOCARDIOGRAPHY

This infant with cyanosis and significant systemic

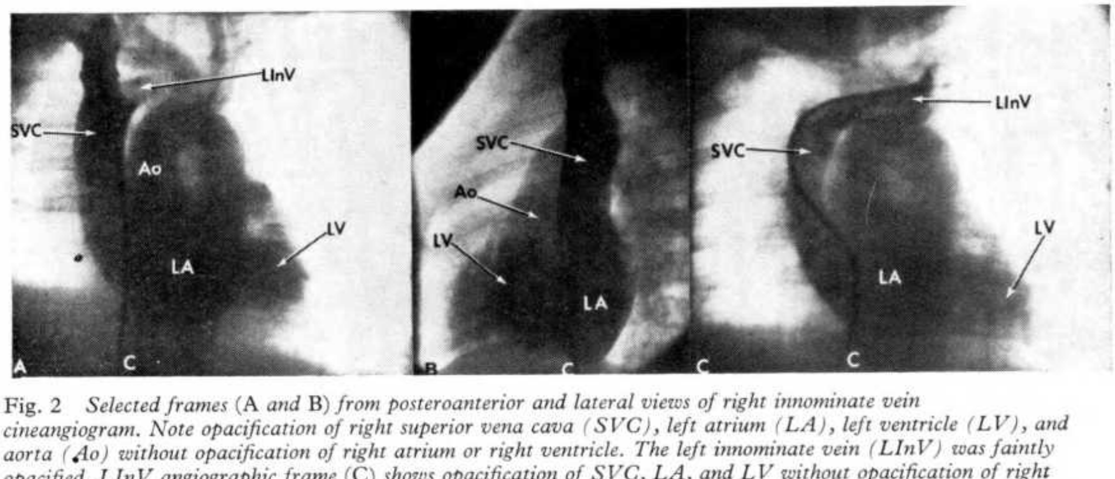

Fig. 2 *Selected frames* (A *and* B) *from posteroanterior and lateral views of right innominate vein cineangiogram. Note opacification of right superior vena cava (SVC), left atrium (LA), left ventricle (LV), and aorta (Ao) without opacification of right atrium or right ventricle. The left innominate vein (LInV) was faintly opacified. LInV angiographic frame* (C) *shows opacification of SVC, LA, and LV without opacification of right atrium or ventricle. There was no opacification of a left superior vena cava. C, catheter.*

arterial desaturation and no other abnormal cardiac findings presents an interesting differential diagnosis[15] which includes pulmonary arteriovenous fistula, pulmonary arterial connection to the left atrium, and anomalous systemic venous connection to the left atrium. We used the contrast echocardiographic technique to aid in this differential diagnosis. In patients with pulmonary arteriovenous fistula or pulmonary artery connection to the left atrium, one would expect appearance of contrast echoes in the right ventricle before being seen in the left atrium, left ventricle, or aorta. Furthermore, in these entities there is no anatomical basis for differential echo contrast opacification when saline was injected into the veins of the hands and foot. Contrast visualisation of the right ventricle and right ventricular outflow tract with injection into the foot in this infant suggested a normal venous drainage of the lower part of the body. Opacification of the left atrium, left ventricle, and aorta without opacification of the right ventricle and right ventricular outflow tract with injection into both hands suggested drainage of the upper part of the body into the left atrium. Thus, with the use of these contrast echocardiographic studies, we were able to arrive at the diagnosis of anomalous systemic venous connection to the left atrium before cardiac catheterisation and selective cineangiography. It could not be determined, however, whether an isolated right superior vena cava or persistent left superior vena cava alone was present or whether both were present.

ANOMALOUS SYSTEMIC VENOUS CONNECTION TO LEFT ATRIUM

Although anomalous systemic venous connection to the left atrium in association with other congenital heart defects[16 17] or with asplenia-polysplenia syndromes[18 19] is well documented, it is rare as an isolated anomaly. To our knowledge, there are only four reported cases of isolated anomalous connection of the right superior vena cava to the left atrium.[20–23] The case reported in this paper is the fifth case of isolated right superior vena cava connection to left atrium. The pertinent features of these five cases are given in Table 2. All but one were children at the time of first presentation with symptoms. The lone exception was a 34-year-old woman reported by Park *et al.*[23] All cases including ours were female and, therefore, it is tempting to postulate a definite sex predilection for this anomaly We hasten, however, to add that this apparent sex predilection is probably related to the small number of cases reported and is a rare coincidence. The presenting symptom was cyanosis in all patients, with exertional dyspnoea in two. Physical examination with the exception of cyanosis was by and large normal. Neck vein distension was noted in one case.[22] This finding may be attributed to severe dilatation of the superior vena cava observed by angiography and at operation. But the cause of the dilatation was not determined.[22]

Chest *x*-rays were normal, as were electrocardiograms except for one case in which the electrocardiogram was interpreted as left ventricular

Table 2 *Summary of reported cases of right superior vena cava to left atrium*

Author	*Age (y) and sex*	*Presenting symptoms*	*Physical examination*	*X-ray*	*Electrocardiogram*	*Diagnosis*	*Surgery*
Wood[20]	10, F	Cyanosis and exercise intolerance	Single 2nd sound	Normal	LVH*	Angiography	Not recommended
Kirsh *et al.*[21]	2, F	Cyanosis	Clubbing	? RV hypoplasia	Normal	Angiography and surgery	Successful correction
Braudo *et al.*[22]	3, F	Cyanosis and growth retardation	Clubbing, neck vein distension, ejection click, and murmur	Normal	Normal	Angiography and surgery	Successful correction
Park *et al.*[23]	34, F	Cyanosis and dyspnoea on exertion	Normal	Normal	Non-specific, ST, T wave changes	Angiography	Refused by patient
Present case	8/12, F	Cyanosis	Normal	Normal	Normal	Angiography	Awaiting surgery

* See the text.
LVH, left ventricular hypertrophy; RV, right ventricle.

hypertrophy.[20] The voltage criteria used,[20] however, would not meet the current criteria.[24] Moderate degrees of polycythaemia and arterial unsaturation were present in cases in which these data were reported. Diagnosis was made by angiography in all and in two cases [21 22] the diagnosis was also substantiated at operation. The role of contrast echocardiography in the diagnosis of this anomaly need not be re-emphasised and indeed it was the major purpose for reporting this case. Nuclear angiography would also be helpful in delineating these anomalies.[23] Though cardiac catheterisation and angiography remain the most useful procedures to confirm the diagnosis, they are not without hazard; use of these anomalous venous channels for catheterisation has been reported to produce paroxysmal supraventricular tachycardia, occasional angina, shock, and cardiac arrest.[25 26]

The cases reported by Kirsh *et al.*[21] and Braudo *et al.*[22] had successful surgical correction. Operation was refused by the patient described by Park and associates[23] and it was not recommended in Wood's case.[20]

A 15-year-old child was reported by Tuchman *et al.*[27] in whom the superior vena cava entered the left atrium. This was first diagnosed by cardiac catheterisation with subsequent confirmation at necropsy. It was not clear, however, from the description whether it was a left or right superior vena cava.[23] Other types of "isolated" anomalous systemic venous connections to the left atrium are also rare and include persistent left superior vena cava into the left atrium,[16 28–33] inferior vena cava into the left atrium,[15 34–36] and total anomalous systemic venous drainage into the left atrium.[37]

EMBRYOLOGICAL ORIGIN

In an attempt to explain the origin of the right superior vena cava to left atrium, persistence of the cephalic portion of the right valve of the sinus venosus[22] and leftward and cephalic displacement of the right horn of sinus venosus[21 23] have been postulated. Misplaced interatrial septum as a cause for this anomaly was mentioned[21 22] but was excluded on the basis that the orifice of the inferior vena cava and coronary sinus would also be located on the left atrial side of the septum if this occurred.[21 22] More than normal leftward or cephalic displacement of the sinus venosus postulated by Kirsh and associates[21] may not produce this anomaly unless associated with a shift of the embryological interatrial septae (septum spurium, primum, and secundum) to the right of (or caudal to) the common cardial vein. Persistence of the cephalic portion of the right valve of the sinus venosus as suggested by Braudo *et al.*[22] may not be tenable because this would also result in the entrance of the inferior vena cava and even the coronary sinus into the left atrium.

An orderly sequence of events with precise timing is necessary for normal development of the cardiac structures. If, for some reason, the sinus venosus becomes incorporated into the right atrium sooner than normal or if the right horn of the sinus venosus grows in a vertical direction (with resultant increase in relative distance between the superior and inferior vena cava) earlier than normal, the cephalic continuation of the venous valves, the septum spurium, and thereafter the septum primum and secondum may come to lie on the right of (or caudal to) the superior vena cava and thereby result in right superior vena cava to left atrium. Alternatively, later than normal timing of development of venous valves and septum spurium (septum primum and secundum to follow) may similarly result in the above-described phenomenon. Though this hypothesis may appear reasonable on theoretical grounds, no evidence to support this hypothesis could be provided from the reported cases.

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References

1 Gramiak R, Shah PM. Echocardiography of the aortic root. *Invest Radiol* 1968; **3:** 356–66.

2 Gramiak R, Shah PM, Kramer DH. Ultrasound cardiography: contrast studies in anatomy and function. *Radiology* 1969; **92:** 939–48.

3 Feigenbaum H, Stone JM, Lee DA, Nasser WK, Chang S. Identification of ultrasound echoes from the left ventricle by use of intracardiac injections of indocyanine green. *Circulation* 1970; **41:** 615–21.

4 Pieroni D, Varghese PJ, Rowe RD. Echocardiography to detect shunt and valvular incompetence in infants and children (abstract). *Circulation* 1973; **48**, suppl IV: 81.

5 Kerber RE, Kloschos JM, Lauer RM. Use of an ultrasonic contrast method in the diagnosis of valvular regurgitation and intracardiac shunts. *Am J Cardiol* 1974; **34:** 722–7.

6 Valdes-Cruz LM, Pieroni DR, Roland JMA, Varghese PJ. Echocardiographic detection of intracardiac right-to-left shunts following peripheral vein injections. *Circulation* 1976; **54:** 558–62.

7 Valdes-Cruz LM, Pieroni DR, Roland JMA, Shematek JP. Recognition of residual postoperative shunts by contrast echocardiographic techniques. *Circulation* 1977; **55:** 148–52.

8 Duff DF, Gutgesell HP. The use of saline for ultrasonic detection of right-to-left shunt in postoperative period (abstract). *Am J Cardiol* 1976; **37:** 132.

9 Seward JB, Tajik AJ, Hagler D, Ritter PG. Peripheral venous contrast echocardiography. *Am J Cardiol* 1977; **39**: 202–12.

10 Seward JB, Tajik AJ, Spangler JG, Ritter DG. Echocardiographic contrast studies. Initial experience. *Mayo Clin Proc* 1975; **50**: 163–92.

11 Seward JB, Tajik AJ, Hagler DJ, Ritter DG. Contrast echocardiography in single or common ventricle. *Circulation* 1977; **55**: 513–9.

12 Serwer GA, Armstrong BE, Anderson PAW, Sherman D, Benson DW Jr, Edwards SB. Use of contrast echocardiography for evaluation of right ventricular hemodynamics in the presence of ventricular septal defects. *Circulation* 1978; **58**: 327–36.

13 Meyer RA. *Pediatric echocardiography*. Philadelphia: Lea & Febiger, 1977: 57–92.

14 Rees AH, Rao PS, Rigby JJ, Miller MD. Echocardiographic estimation of a left-to-right shunt in isolated ventricular septal defects. *Eur J Cardiol* 1978; **7**: 25–33.

15 Meadows WR, Bergstrand I, Sharp JT. Isolated anomalous connection of a great vein to the left atrium: the syndrome of cyanosis and clubbing "normal" heart, and left ventricular hypertrophy, on electrocardiogram. *Circulation* 1961; **24**: 669–76,

16 Friedlich A, Bing RJ, Blount SG Jr. Physiological studies in congenital heart disease: IX Circulatory dynamics in the anomalies of venous return to the heart including pulmonary arteriovenous fistula. *Bull Johns Hopkins Hosp* 1950; **86**: 20–57.

17 Winter FS. Persistent left superior vena cava: survey of world literature and report of thirty additional cases. *Angiology* 1954; **5**: 90–132.

18 Raghib G, Ruttenberg HD, Anderson RC, Amplatz K, Adams P Jr, Edwards JE. Termination of left superior vena cava in left atrium, atrial septal defect and absence of coronary sinus: a developmental complex. *Circulation* 1965; **31**: 906–18.

19 Rao PS, Leonard T. Polysplenia syndrome. *Cardiol Digest* 1976; **11**: 14–22 (March).

20 Wood P. *Diseases of the heart and circulation*. 2nd ed. London: Eyre & Spottiswood, 1956: 457–8.

21 Kirsch WM, Carlsson E, Hartmann AF Jr. A case of anomalous drainage of the superior vena cava into the left atrium. *J Thorac Cardiovasc Surg* 1961; **41**: 550–6.

22 Braudo M, Beanlands DS, Trusler G. Anomalous drainage of the right superior vena cava into the left atrium. *Can Med Assoc J* 1968; **99**: 715–9.

23 Park HM, Smith ET, Silberstein EB. Isolated right superior vena cava draining into left atrium diagnosed by radionuclide angiocardiography. *J Nucl Med* 1974; **14**: 240–2.

24 Liebman J, Plonsey R. Electrocardiography. In: Moss AJ, Adams FH, Emmanouilides GC, eds. *Heart disease in infants, children and adolescents*. 2nd ed. Baltimore: Williams & Wilkins, 1977: 18–61.

25 Rao PS, Molthan ME. Systemic venous anomalies and partial heterotaxia with normal heart. *Am J Dis Child* 1973; **125**: 749–52.

26 Rowe RD: Anomalies of venous return. In: Keith JD, Rowe RD, Vlad P, eds. *Heart disease in infancy and childhood*. 3rd ed. New York: Macmillan, 1978: 554–88.

27 Tuchman H, Brown JF, Huston JH, Weinstein AB, Rowe GG, Crumpton CW. Superior vena cava draining into left atrium: another cause for left ventricular hypertrophy with cyanotic congenital heart disease. *Am J Med* 1956; **21**: 481–4.

28 Ödman P. A persistent left superior vena cava communicating with the left atrium and pulmonary vein. *Acta Radiol* 1953; **40**: 554–60.

29 Davis WH, Jordaan FR, Snyman HW. Persistent left superior vena cava draining into the left atrium as an isolated anomaly. *Am Heart J* 1959; **57**: 616–22.

30 Fraser RS, Dvorkin J, Rossall RE, Eidem R. Left superior vena cava. A review of associated congenital heart lesions, catheterization data and roentgenologic findings. *Am J Med* 1961; **31**: 711–6.

31 Meadows WR, Sharp JT. Persistent left superior vena cava draining into the left atrium without arterial oxygen unsaturation. *Am J Cardiol* 1965; **16**: 273–9.

32 Taybi H, Kurlander GJ, Lurie PR, Campbell JA. Anomalous systemic venous connection to the left atrium or to a pulmonary vein. *Am J Roentgenol* 1965; **94**: 62–77.

33 Sherafat M, Friedman S, Waldhausen JA. Persistent left superior vena cava draining into the left atrium with absent right superior vena cava. *Ann Thorac Surg* 1971; **11**: 160–4.

34 Gardner DL, Cole L. Long survival with inferior vena cava draining into left atrium. *Br Heart J* 1955; **17**: 93–7.

35 Gautam HP. Left atrial inferior vena cava with atrial septal defect. *J Thorac Cardiovasc Surg* 1968; **55**: 827–29.

36 Kim YS, Serratto M, Long DM, Hastreiter AR. Left atrial inferior vena cava with atrial septal defect. *Ann Thorac Surg* 1971; **11**: 165–70.

37 Viart P, LeClerc JL, Primo G, Polis O. Total anomalous systemic venous drainage. *Am J Dis Child* 1977; **131**: 195–8.

Requests for reprints to Professor P Syamasundar Rao, Department of Pediatrics, Medical College of Georgia, Augusta, Georgia, 30912, USA.

Br Heart J 1980; **44:** 724

Massive dilatation of the left atrium

Sir,
It is accepted that left recurrent laryngeal nerve paralysis in association with massive dilatation of the left atrium is caused by compression between the aortic arch and pulmonary artery by upward displacement of the latter.

The cause of dysphagia in these circumstances is less clear. Morgan and Mourant[1] suggest that it is the result of disordered peristalsis consequent upon stretching of autonomic nerve fibres between the posterior pulmonary plexuses and the oesophagus with possible damage to nerves supplying the oesophageal plexus. This is an ingenious explanation. Five of our 15 patients with massive atrial dilatation complained of difficulty in swallowing solid food and two of these also complained of difficulty in swallowing liquids.[2] One had painful dysphagia after swallowing a large bolus. Two patients pointed to the site of the obstruction at the suprasternal notch and the xiphisternum, respectively, whereas in all, fluoroscopy after a barium swallow showed the obstruction to be a few centimetres below the tracheal bifurcation.

While increased left atrial pressure in mitral valve disease is not likely to exceed peak intra-oesophageal pressure during active peristalsis, the displacement and narrowing of the oesophagus is considered sufficient to lead to dysphagia. In addition, widening of the carinal angle has led to oesphageal indentation by the left main bronchus.

Most patients with massive atrial dilatation are in atrial fibrillation, but even in the absence of a normally pulsating atrium the pressure exerted is sufficient to erode vertebrae.

Raymond Daley,
The White House,
The Green,
Woodchurch,
Ashford, Kent.

References

1 Morgan AA, Mourant AJ. Left vocal cord paralysis and dysphagia in mitral valve disease. *Br Heart J* 1980; **43:** 470–3.
2 Daley R, Franks R. Massive dilatation of the left auricle. *Q J Med* 1949; NS **18:** 81–91.

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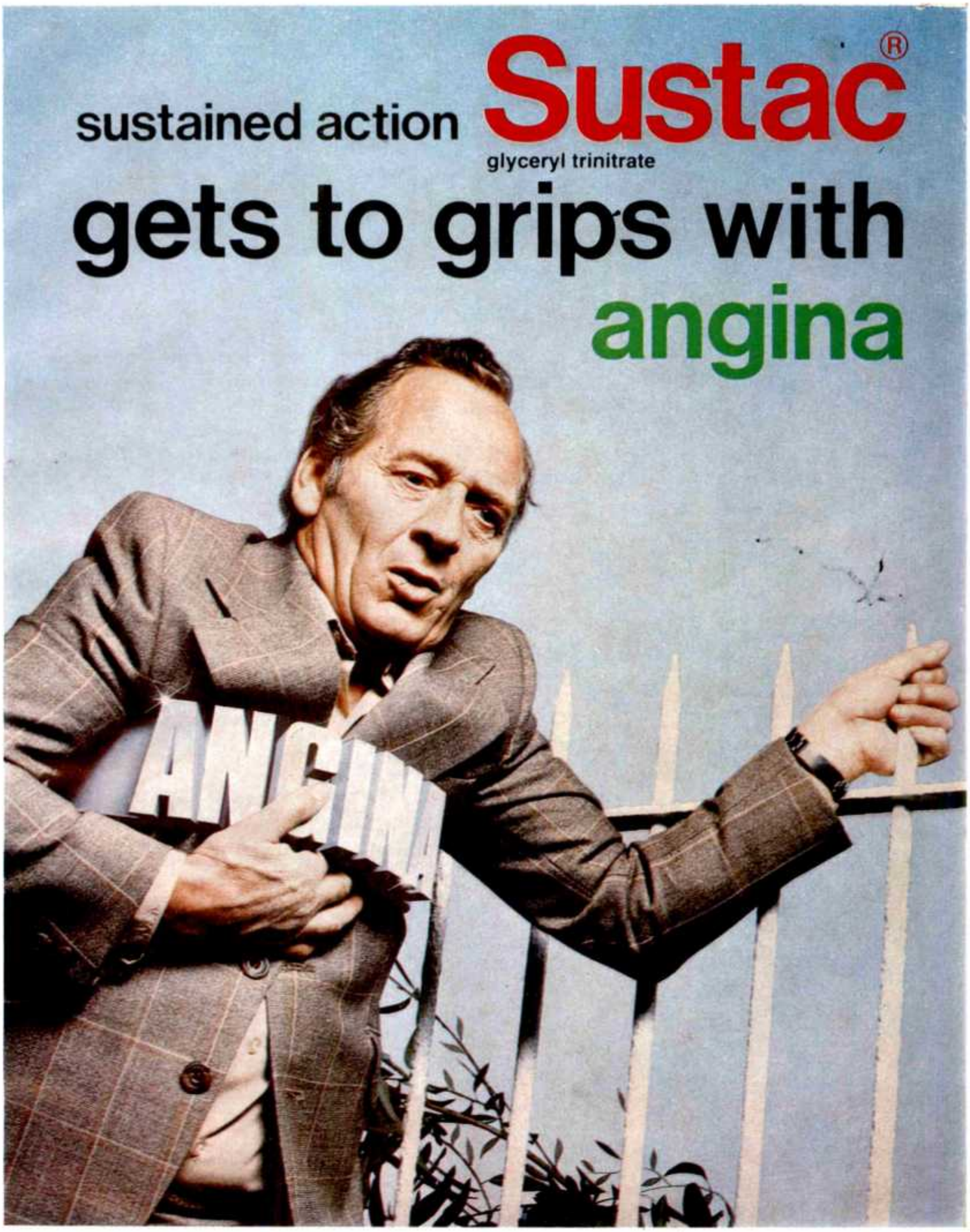

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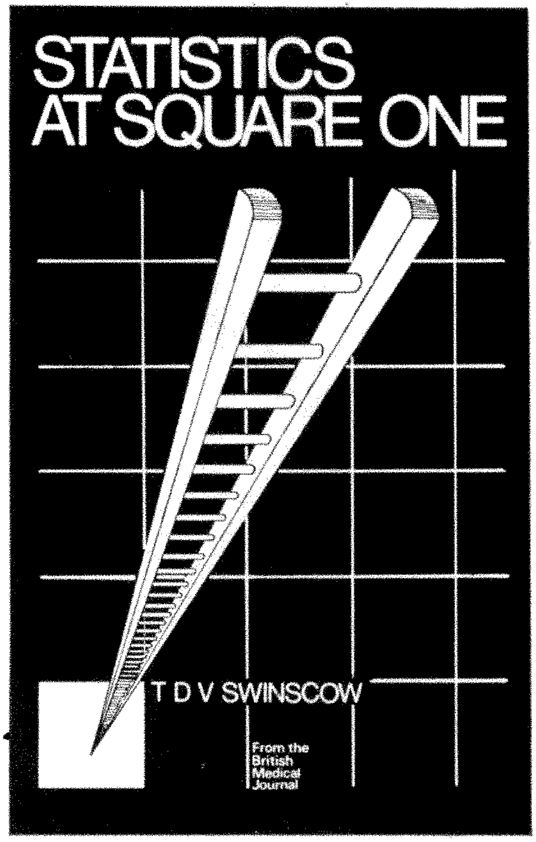

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